

Clinical characteristics of aggressive Non-Hodgkin lymphoma with emphasis on the role of positron emission tomography/computed tomography in assessment of treatment response: a retrospective study

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Original Article

Abstract

Purpose: The purpose of this study was to evaluate the role of post-treatment Positron Emission Tomography/Computed Tomography (PET/CT) in aggressive non-Hodgkin's lymphoma (NHL) with regard to the clinical and treatment characteristics and disease-free survival (DFS). **Methods:** We retrospectively studied charts of 30 patients with aggressive NHL who had PET/CT only after completion of treatment. **Results:** Thirty patients received CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or Rituximab (R)-CHOP (22 and 8 patients respectively), followed by radiotherapy in 19/30 patients (63.3%). Following 3-4 cycles of chemotherapy, interim CT showed regressive, stationary and progressive disease in 18, 10, 2 (60%, 33.3%, 2%) patients respectively. PET/CT was performed 4-6 weeks after end of treatment. 22/30 (73.3%) patients had negative scan, of whom 13 (59.1%) patients remained in remission till the end of the study while 9 patients relapsed after a median DFS of 12 months. PET/CT was positive in 8/30 (26.7%) patients who had refractory disease. PET/CT scan had sensitivity of 75%, specificity of 72.7%, negative predictive value (NPV) of 88.9%, and positive predictive value (PPV) of 50%. **Conclusion:** PET/CT has an important role in end-of-therapy response evaluation in fluorodeoxyglucose (FDG)-avid aggressive NHL. It proves high sensitivity and specificity in detection of residual disease and provides an accurate indication of overall survival and disease-free survival. CT continues to have an important role in post-treatment response assessment whether as a single modality or in combination with PET scan.

Keywords: Aggressive NHL, Post-therapy, PET/CT, Disease-free survival.

1. Introduction

Despite the increasing annual incidence of NHL, the overall 5-year survival (ORS) rate is steadily improving. This is partly due to advances in treatment regimens which achieve remission rates with less patient toxicity.¹ In adults the most common subtypes of NHL are follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL), which account for more than 50% of NHL.^{2,3} Histologically NHL is classified into indolent, aggressive, and highly aggressive subtypes. Prognosis

and treatment options of NHL depend on the disease stage, grade, and the histologic subtype.

DLBCL is the most common subtype of NHL accounting for 30 - 35% of all newly diagnosed cases and more than 80% of aggressive NHL⁴, followed by mantle cell lymphoma (MCL) and adult T-cell leukemia/lymphoma which represent about 6 and 8% of NHL respectively.⁵ DLBCL has a heterogeneous outcome where almost half of the patients are incurable due to poor response to

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treatment and die because of the disease.⁶ Many patients with DLBCL initially respond to R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone), however the 5-year overall survival rates for these patients range from 45% to 82% due to the heterogeneous nature of this disease.⁷

The combined use of PET and CT has higher sensitivity and specificity due to the combined benefit of anatomic and functional imaging in the initial staging, restaging, and assessment of response to therapy in hematologic malignancies as compared to FDG-PET and CT alone. Aggressive NHL such as DLBCL, grade III FLs, MCL have moderate to high F-FDG uptake with a sensitivity of 85-100%.⁸ PET/CT is considered a standard imaging modality in B-cell aggressive NHL which can accurately diagnose, assess the treatment response, and estimate the prognosis.^{9,10} End-of-treatment PET/CT is used to evaluate the efficacy of treatment, to follow-up residual tumor, and to select treatment.^{9,11} The follow-up PET/CT in NHL has 90% sensitivity and 88% specificity. A positive PET/CT scan at the end of treatment is a strong indicator of poor survival where the risk for disease relapse increases.¹² This residual positivity has been incorporated into revised response criteria for aggressive lymphoma.¹³ Patients with negative post-treatment scan have excellent prognosis.¹²

Spaepen *et al.*¹⁴ showed that 56 of 67 NHL patients had negative scans after end of first line treatment, and remained in complete remission at a median follow-up duration of 653 days whereas the 26 patients who had a positive scan developed relapse at a median of 73 days. According to the authors the PET scan ability to identify a residual aggressive disease after completion of the first line chemotherapy had a NPV of 80% and a PPV of 100%. Similarly studies involving more than 300 patients diagnosed with aggressive NHL, reported consistently high NPV 80% to 100% and a lower PPV of 50% to 100%.¹⁵⁻¹⁹ PET/CT is currently recommended in DLBCL to improve the accuracy of staging and end of treatment evaluation.²⁰ Recently clinical trials focus on the prognostic role of early interim PET/CT after few cycles of chemotherapy to guide response-adapted treatment.²¹ A meta-analysis by Terasawa *et al.*²², demonstrated that PET/CT had a sensitivity of 81% and a specificity of 97% for advanced-stage Hodgkin's lymphoma (HL), and a sensitivity of 78% and a specificity of 87% for DLBCL. More recent studies in DLBCL reported good NPV versus more variable PPV.^{9,21} The role of interim PET/CT in aggressive NHL remains unclear compared to HL where some studies report better overall survival and disease free survival associated with a negative interim PET/CT, while other studies have not confirmed these results partly due to the variety of interpretation criteria used.^{15,23,24} In advanced FL, post-treatment PET seems to better predict outcome than interim PET.²⁵ Interim PET/CT

should not be used to guide treatment and is recommended in the setting of clinical trials.²⁰

To standardize the PET/CT interpretation criteria for lymphoma between different centers the International Harmonization Project (IHP) criteria were developed where the mediastinal blood pool uptake was used as a reference background to define positive PET/CT by detecting a residual mass 2 cm or more.²⁶ The IHP criteria which are incorporated into the Standard Response Criteria²⁰ are commonly used in evaluation of end-of-treatment PET scans. The Deauville criteria further improved the interpretation criteria of PET/CT scans by using a five-point scale to assess the FDG uptake in the involved site relative to that of the mediastinum and the liver.²⁷ This scale is agreeable and increasingly used for interpreting therapy response in DLBCL and FL.^{28,25,29} The five-point scale has been incorporated into the updated standard response criteria for lymphoma (The Lugano Classification).³⁰ Standardized uptake value (SUV) is a third approach which has been adopted as an interpretation criteria to help reduce false-positivity of interim PET/CT and to improve prognostic value in NHL. It is a semi quantification of FDG uptake using the maximum SUV (SUV max) at baseline and midtherapy. Other quantitative variables for response evaluation under study include the change in maximum SUV (Δ SUV max), Δ SUV mean, total lesion glycolysis, and metabolic tumor volume.³¹

In this study we aimed to evaluate the role of post-treatment PET/CT in aggressive NHL with regard to the clinical and treatment characteristics and DFS.

2. Methods and Materials

Between January 2012 and December 2014 we retrospectively reviewed the charts of pathologically proven aggressive NHL patients treated at Nasser Institute for Research and Cancer Treatment and at the department of Clinical Oncology, Ain-Shams University. The charts were examined after obtaining the approval of the Research Ethical Committee, Faculty of Medicine, Ain-Shams University.

Thirty patients fulfilled the inclusion criteria which included both sexes, age from 18-65 years old, Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, newly diagnosed and previously treated patients with biopsy proven diagnosis of aggressive NHL. Staging of lymphoma was done according to the Ann Arbor staging system (National Comprehensive Cancer network (NCCN) 2011).³² Risk factor evaluation was done using the International NHL Prognostic Factors Project (IPI).³³ All the patients had interim CT which showed evidence of disease.

First line treatment consisted of 6-8 cycles of CHOP or Rituximab (R) plus CHOP and/or radiotherapy. Complete patient history and relative examination data were collected at each visit. Only end-of-treatment PET/CT was performed, no pre-treatment or interim PET/CT was done due to the financial costs.

2.1 Statistical Analysis

Data were analyzed using the Statistical Package for Social Science (IBM SPSS) version 20 for Windows (SPSS, Chicago, IL, USA). Disease-free survival was defined as the interval from the date of remission to the date of disease progression or first relapse. The correlation of post-therapy negative and positive PET/CT residual masses with the different patient and treatment characteristics was analyzed using Chi-square test. Kaplan–Meier test and Log-rank test were used to analyze the correlation of DFS with negative and positive PET/CT scans. The comparison between patients with negative and positive PET/CT scans regarding quantitative data was done using the Independent *t*-test. *P* value of < 0.05 was considered to be statistically significant.

3. Results

Thirty patients fulfilled the eligibility criteria and their characteristics are summarized in (Table 1). The age ranged from 30-86 years with a slight female predominance (18/30, 53.3%). Following completion of therapy, response was evaluated by PET/CT imaging which was negative in 22/30 (73.3%) and positive in 8/30 patients (26.7%). As regards performance status, 16/22 (72.7%) patients with negative PET/CT scan had an ECOG 1, compared to ECOG 2 in 5/8 (62.5%) of patients with positive PET/CT imaging (*p* 0.024). Associated comorbidities mainly hypertension and diabetes mellitus were more common in patients who

had positive post-therapy PET/CT scan (75%) than in patients with negative PET/CT scans (27.3%) (*p* 0.018).

The majority of the patients had stage II and III disease 63.7% and 75% respectively (*p* 0.615). DLBCL was the most common histologic subtype 93.3%. Most of the patients with negative post-therapy PET/CT scan had intermediate and high risk IPI (45.5% each), while 62.5% of patients with positive PET/CT scan had intermediate risk IPI (*p* 0.6). The studied cohort was treated with CHOP as first line treatment (73.3%) and received no radiotherapy in (63.3%) of patients. Following 3-4 cycles of chemotherapy, interim CT scan showed regressive disease in 16/30 (72.7%) of patients who later had negative post-therapy PET/CT scans, while interim CT showed regressive disease in 2/30 (25%) of patients who had a positive PET/CT scan by the end of treatment. By the end of therapy, response assessment was performed by PET/CT scan which was negative in (22/30, 73.3%) and positive in 8/30 of patients. Remission was achieved in 59.1% and 40.9% of patients who had negative PET/CT relapsed, whereas 100% of patients with positive PET/CT scan had refractory disease (*p* 0.000) (Table 2, 3).

The effect of clinical and treatment factors on the result of post-treatment PET/CT was studied (Table 4). Nodal disease was the most common disease site in both positive and negative PET/CT scans (59.1%, 75%) respectively. 16/22 (72.7%) of PET negative patients and 6/8 (75%) of PET positive patients received CHOP chemotherapy (*p* 0.9). A significant correlation between some of the clinical factors and result of the end-of-treatment PET/CT was detected namely sex (*p* 0.024), ECOG status (*p* 0.024) and associated comorbidities (*p* 0.018).

Table 1: Clinical characteristics

	Variable	Total no. 30
Sex	Male	14 (46.7%)
	Female	16 (53.3%)
Age	Mean ± SD	48.47 ± 10.90
	Range	30 – 86
ECOG PS	0	3 (10%)
	1	19 (63.3%)
	2	8 (26.7%)
Comorbidities	No	18 (60.0%)
	Yes	12 (40.0%)

Subtype	DLBC	28 (93.3%)
	Follicular	1 (3.3%)
	T- cell	1 (3.3%)
Stage	1	4 (13.3%)
	2	9 (30.0%)
	3	11 (36.7%)
	4	6 (20.0%)
Site of disease	Nodal	19 (63.3%)
	Extra-nodal	8 (26.7%)
	Spleen	3 (10.0%)
A/B	No symptoms	27 (90.0%)
	Positive symptoms	3 (10.0%)
LDH	Mean±SD	376.23 ± 87.79
	Range	198 – 570
Hemoglobin	Mean±SD	11.42 ± 1.25
	Range	8.6 – 14.1
Leukocytosis	Mean±SD	9.84 ± 5.99
	Range	4.3 – 18.9
IPI	Low	3 (10.0%)
	Low-Intermediate	15 (50.0%)
	Intermediate-High	12 (40.0%)

PS: performance status, SD: standard deviation, LDH: lactate dehydrogenase enzyme, IPI: international prognostic index

Table 2: Primary Treatment Characteristics

Variable	Table no. 30	
Chemotherapy	CHOP	22 (73.3%)
	R-CHOP	8 (26.7%)
Number of cycles	Mean ± SD	6.47 ± 0.86
	Range	6-8
Radiotherapy	NO	19 (63.3%)
	Yes	11 (36.7%)
Interim CT (after 3-4 cycles)	Complete response	2 (0.6%)
	Regressive	16 (53.3%)
	Stationary	10 (33.3%)
	Progressive	2 (0.6%)
End-of- treatment PET/ CT	Negative	22 (73.3%)
	Positive	8 (26.7%)
Response	Remission	13 (43.3%)
	Relapse	9 (30%)
	Refractory	8 (26.7%)

Table 3: Result of PET/CT scan at end-of-treatment

End-of-treatment PET		Negative PET		Positive PET		Chi-square test	
		No.	%	No.	%	X ²	P-value
Response	Remission	13	59.1%	0	0%	20.649	0.000
	Relapsed	9	40.9%	0	0%		
	Refractory	0	0.0%	8	100%		

Table 4: Relation between clinical data and end-of-treatment PET/CT scan

Post therapy PET/CT		Negative PET		Positive PET		Chi-square test	
		No = 22		No = 8		X ² /t*	P-value
Sex	Male	13 (59.1%)		1 (12.5%)		5.117	0.024
	Female	9 (40.9%)		7 (87.5%)			
Age	Mean ± SD	49.45 ± 11.49		45.75 ± 9.19		-0.819	0.420
	Range	30 – 86		36 – 58			
ECOG PS	0	3 (13.6%)		0 (0.0%)		1.212	0.024
	1	16 (72.7%)		3 (37.5%)			
	2	3 (13.6%)		5 (62.5%)			
Comorbidities	No	16 (72.7%)		2 (25.0%)		5.568	0.018
	Yes	6 (27.3%)		6 (75.0%)			
Subtype	DLBC	20 (90.9%)		8 (100.0%)		0.779	0.677
	Follicular	1 (4.5%)		0 (0.0%)			
	T-cell	1 (4.5%)		0 (0.0%)			
Stage	1	4 (18.2%)		0 (0.0%)		1.798	0.615
	2	6 (27.3%)		3 (37.5%)			
	3	8 (36.4%)		3 (37.5%)			
	4	4 (18.2%)		2 (25.0%)			
Site of disease	Nodal	13 (59.1%)		6 (75.0%)		1.337	0.513
	Extra-nodal	6 (27.3%)		2 (25.0%)			
	Spleen	3 (13.6%)		0 (0.0%)			
A/B	No symptoms	20 (90.9%)		7 (87.5%)		0.076	0.783
	Positive symptoms	2 (9.1%)		1 (12.5%)			
IPI	Low	2 (9.1%)		1 (12.5%)		1.023	0.600
	Low-Intermediate	10 (45.5%)		5 (62.5%)			
	Intermediate-High	10 (45.5%)		2 (25.0%)			

* Independent t-test P > 0.05 NS, P < 0.05: S, P < 0.01: HS

Chemotherapy was associated with negative PET/CT ($p \geq 0.05$). 9/22 patients who received radiotherapy had negative PET/CT ($p \geq 0.05$). Interim CT was the only treatment-related factor that significantly affected the result of post-therapy PET/CT (p 0.013) (Table 5).

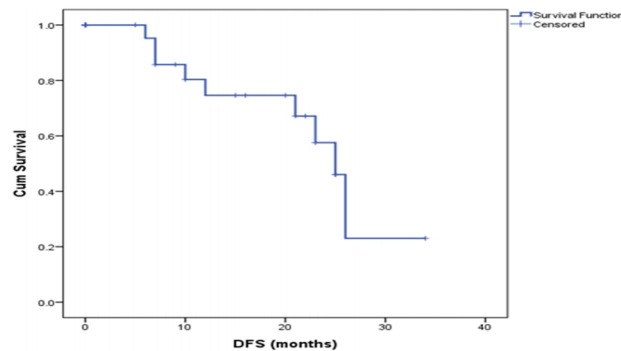
Table 5: Relation between type of treatment and end-of-treatment PET/CT

End-of-treatment PET/CT		Negative PET	Positive PET	Chi-square test	
		No = 22	No = 8	X^2/t^*	P-value
Chemotherapy	CHOP	16 (72.7%)	6 (75.0%)	0.015	0.901
	R-CHOP	6 (27.3%)	2 (25.0%)		
Number of cycles	Mean \pm SD	6.45 \pm 0.86	6.50 \pm 0.93	0.126	0.901
	Range	6 – 8	6 – 8		
Radiotherapy	No	13 (59.1%)	6 (75.0%)	0.639	0.424
	Yes	9 (40.9%)	2 (25.0%)		
Interim CT	Regressive	16 (72.7%)	2 (25.0%)	8.636	0.013
	Stationary	6 (27.3%)	4 (50.0%)		
	Progressed	0 (0.0%)	2 (25.0%)		

13/22 (59.1%) patients remained in remission till the end of the study follow-up duration and had a median DFS of 20 months. Whereas 9/22 (40.9%) patients relapsed after a median DFS of 12 months. Eight/30 patients had a refractory disease (26.7%) and a positive post-treatment PET/CT. The median DFS for all the studied patients was 25 months (95% CI 22.5 - 27.5) (Table 6, Figure 1).

Table 6: Disease-free survival of the study cohort (n=30)

	Median	Standard Error	95% Confidence Interval	
			Lower Bound	Upper Bound
DFS (months)	25	1.281	22.49	27.51

**Figure1:** Disease-free survival (n=30)

The prognostic factors that significantly influenced the DFS were site of disease (p 0.017), presence or absence of B symptoms (p 0.017) and type of chemotherapy (p 0.045). The overall survival was 100% (Table 7, Figures 2, 3).

Table 7: Prognostic factors of disease-free survival

		Count	Median	DFS (months)			Log rank test	
				SE	95% Confidence Interval	X ²	P-value	
PS	0	3						
	1	(19)	28	4.12	19.93	36.08	0.624	0.429
	2	(8)	21	4.08	13.00	29.00		
Comorbidities	No	18	26	5.55	15.12	36.88	0.041	0.84
	Yes	12	24	2.84	18.44	29.56		
Stage	1	4	29	3.00	23.12	34.88	2.42	0.49
	2	9	24	1.49	21.08	26.92		
	3	11	21	2.39	16.32	25.68		
	4	6	30	0.00	0.00	0.00		
Site of disease	Nodal	19	24	1.56	20.94	27.06	8.111	0.017
	Extra- nodal	8	28	5.39	17.43	38.57		
	Spleen	3	40	0.00	0.00	0.00		
A/B	No symptoms	27	28	2.49	23.13	32.87	5.668	0.017
	Positive symptoms	3	15	0.00	0.00	0.00		
Prognosis	Low	3	23	4.90	13.40	32.60	4.53	0.104
	Low-Intermediate	15	29	0.74	27.55	30.45		
	Intermediate-High	12	21	1.48	18.11	23.89		
Chemotherapy	CHOP	22	28	3.10	21.93	34.07	3.685	0.045
	R-CHOP	8	19	3.00	13.12	24.88		
Radiotherapy	No	19	28	3.01	22.09	33.91	0.369	0.544
	Yes	11	24	2.31	19.48	28.52		
Interim CT	Regressive	18	26	2.47	21.16	30.84	1.064	0.587
	Stationary	10	28	5.24	17.74	38.27		
	Progressed	2	15	0.00	0.00	0.00		
Salvage	No	14	21	3.12	14.89	27.11	1.906	0.592
	ICE	8	29	0.82	27.40	30.60		
	DHAP	5	23	0.00	0.00	0.00		
	Others	3	0	0.00	0.00	0.00		

ICE: ifosfamide, carboplatin, etoposide, DHAP: dexamethasone, high dose Ara-C, platinol.

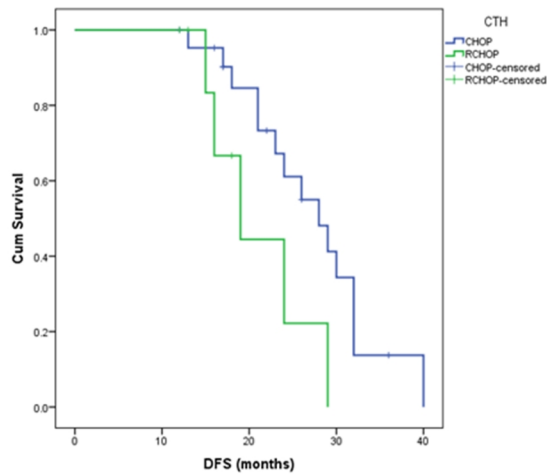


Figure 2: Relation between chemotherapy and DFS

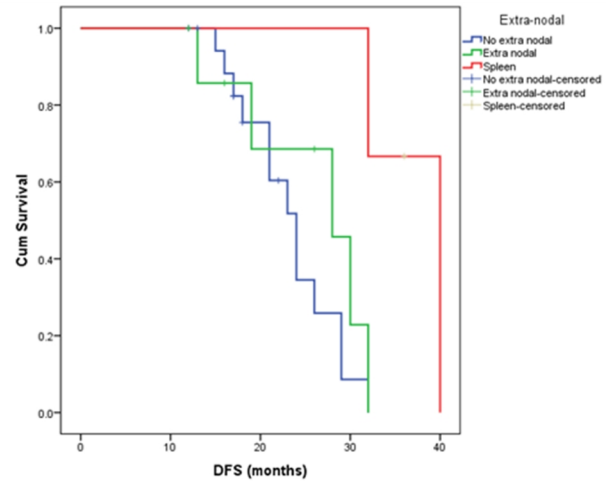


Figure 3: Relation between disease site and DFS

Salvage chemotherapy was indicated in relapsed patients 9/22 with negative PET imaging and all refractory PET positive disease (p 0.106). Chemotherapy included ICE, DHAP, and other regimens in (26.7%, 16.6 %, and 10%) respectively. The number of chemotherapy cycles ranged from 3 to 6 cycles followed by PET/CT scan in only 9 patients (negative scan in 8 and positive in 1 patient). Only one patient with refractory disease required two cycles of second line salvage chemotherapy ESHAP (etoposide, solu-medrol (methylprednisolone), high-dose Ara-C, platinol). Bone marrow transplantation (BMT) was performed in all relapsed patients (Table 8).

Table 8: Salvage Treatment

Post-therapy PET		Negative PET	Positive PET	Chi-square test	
		No = 22	No = 8	χ^2	P-value
Salvage Chemotherapy	No	13 (59.1%)	1 (12.5%)	6.118	0.106
	ICE	5 (22.7%)	3 (37.5%)		
	DHAP	3 (13.6%)	2 (25.0%)		
	Others	1 (4.5%)	2 (25.0%)		
Number of cycles	Mean \pm SD	3.00 \pm 0.00	4.00 \pm 1.67	1.593	0.139
	Range	3 - 4	2 - 6		
Follow up PET	Negative PET	8 (36.4%)	1 (12.5%)	1.591	0.207
	Not done	14 (63.6%)	7 (87.5%)		
Bone marrow transplantation	Not done	14 (63.6%)	6 (75.0%)	0.341	0.559
	Done	8 (36.4%)	2 (25.0%)		

4. Discussion

Response evaluation after treatment of lymphoma serves as a measure of DFS and ORS as well as guides decisions whether to continue or change treatment as shown by many studies.³⁴⁻³⁹ The fundamental limitations of CT are that identification of pathologic lymph nodes is based solely on size, while detection of

bone marrow and extra-nodal tissue involvement may be limited. The integration of PET/CT allowed detection of metabolic activity in non-enlarged lymph nodes as well as high sensitivity to extranodal disease thus improved initial disease staging. PET/CT has the ability to distinguish between residual metabolically active

tumor and necrosis or fibrosis which can be seen as residual by contrast enhancement CT (CECT), so it is very useful to assess end of treatment response.⁴⁰ Also some studies compared CECT to 18 F-FDG PET/CT as regards detection of extranodal lymphoma, where the sensitivity and specificity were around 88% and 100% respectively for PET/CT vs. 50% sensitivity and 90% specificity for CECT.^{41,42} The use of PET for post-treatment response assessment in lymphoma by distinguishing fibrosis or sclerosis from active residual disease is perhaps the most established role of PET in lymphoma.⁴³ FDG-PET/CT has a high PPV for remission assessment. In FDG avid aggressive NHL including DLBCL, the post-treatment PET has a high NPV 90 - 100% and a lower PPV at 50 - 82%.¹⁴⁻¹⁶ The low PPV could be due to the uptake of FDG by inflammation which could be seen after chemotherapy and radiotherapy. So to avoid equivocal results, the post-therapy PET/CT imaging is performed 6 - 8 weeks after the end of treatment²⁰ or at least 3 weeks after completion of chemotherapy and 8 -12 weeks after radiation therapy.⁴⁴ A systematic review of 19 studies by Terasawa *et al.*²² included 254 patients with aggressive NHL; the authors observed that the sensitivity and specificity of PET/CT in predicting relapse ranged from 50 - 70% and 67 - 100%, respectively. Another systematic review by Zijlstra *et al.*¹⁸ included 15 studies with 705 NHL patients; post-treatment PET had 72% and 100% sensitivity and specificity respectively for detection of residual disease. Similarly, our results showed that PET/CT had sensitivity of 75% and specificity of 72.7% in predicting relapse. In agreement with the literature, we demonstrated that PET/CT had a low PPV 50% and high NPV 88.9%. However, our results disagree with that of Abo-Sheisha and Abdel Fattah⁴⁵, they retrospectively studied 62 patients with DLBCL who had CT documented residual masses after completion of chemotherapy. The authors reported that PET scan had higher sensitivity of 100%, a specificity of 91%, a NPV of 100% and a PPV of 77.8%. Lavelly *et al.*³⁷ similarly showed high post- therapy PET scans sensitivity of 100% and specificity of 84% for detection of relapse in their study of 20 NHL patients. The PPV of post-treatment PET in the current study is close to the PPV of 78% reported by Juweid *et al.*²⁶ while our NPV was lower than NPV by the same authors (89% vs. 100% respectively). The sensitivity and specificity of PET/CT has been the subject of debate due to readers and technical aspects of the devices.²⁵ While the clearest role of PET scans in lymphoma is evaluation of response in the end of treatment setting⁴³, CT scan continues to be an important tool to confirm remission status after therapy whether as adjunct to PET or as a single imaging modality in some practices.⁴⁶

Based on the ability of PET to better assess remission in aggressive more than in indolent NHL, the IHP incorporated FDG-PET/CT into the definitions of post-therapy responses.²⁰ This led to better

discrimination of response categories where the complete response CR-unconfirmed category was replaced by complete or partial response based on FDG uptake.³⁴ The shortcoming of the IHP in assessment of response was that FDG avidity was defined relative to the mediastinal blood pool. Subsequently the Deauville criteria were proposed for visually grading FDG PET/CT activity in 2009 based on both mediastinal and liver blood pool.²⁷ In 2014 the Lugano classification was published with the goal of simplification and standardization of response assessment and reporting in lymphoma. It addresses the role of PET/CT for staging, interim and end of treatment response evaluation.³⁰ In the FDG avid HL and aggressive NHL a negative end of treatment FDG-PET scan excludes residual viable tumor with high certainty, however, does not exclude the presence of microscopic disease.³⁷ When a post-treatment CT imaging shows a residual disease more than 2 cm despite a negative PET/CT, the risk of malignancy is higher.⁴⁶

Most of the available data on end-of-treatment PET scans in NHL were published in the pre-rituximab era where PET/CT at the end of therapy in aggressive NHL had a high PPV and NPV. However, in the rituximab era, the incidence of false-positive PET scans seem to be higher making the PPV low and the NPV remains high.⁴⁷ Moskowitz *et al.*⁴⁸ treated 98 patients with DLBCL using a dose-dense R-CHOP-like regimen and interim PET/CT were performed after four cycles. Biopsy of residual disease as detected by positive interim PET scans was done, and it proved that 87% of patients had false positive residual disease. DFS of interim PET-positive/biopsy-negative patients was the same as that in patients with a negative interim PET. The low PPV of the PET scan detected in patients who received rituximab might be due to recruitment of immune cells to the tumor by rituximab which is associated with inflammatory changes.⁴⁸ Juweid *et al.*³⁴ showed that in 29 out of 54 patients who received rituximab, the end of therapy PET had PPV of 68% and NPV of 80%. Han *et al.*⁵⁰ reported on 48 NHL patients who all received rituximab, they observed a low PPV of 19% in follow-up PETs performed for rituximab treated patients, while the NPV remained high at 85%. Avivi *et al.* 2013⁵¹ retrospectively studied 119 patients with newly diagnosed DLBCL, 35 received CHOP and 84 received R-CHOP and the patients underwent 442 follow-up PETs. The patients were followed for a median of 3.4 years, where 31 patients relapsed as detected by PET with no false-negative results (17 vs. 14 respectively, $p = 0.02$). The authors compared the specificity and PPV of PET scans which were significantly lower in patients receiving R-CHOP vs. CHOP (84% vs. 87%, $p = 0.023$; 23% vs. 74%, $p < 0.0001$). This indicated a higher false-positive (FP) rate in subjects receiving R-CHOP (77% vs. 26%, $p < 0.001$) which remained as late as 3 years following completion of treatment. The authors concluded that routine follow-up PET scans is not

recommended in DLBCL patients treated with rituximab and also they recommended identifying strict criteria for performing surveillance PET. In aggressive NHL change of treatment should not be based on a positive PET scan during or after rituximab-based therapy, it must be first confirmed by biopsy. Among the 30 patients we studied, 22 received CHOP, and 8 received R-CHOP. End-of-therapy PET/CT was negative in 16/22 and 6/8 of patients who were treated with CHOP and R-CHOP respectively, and positive in 6/22 patients, 2/8 patients who received CHOP and R-CHOP respectively ($p < 0.9$). Studying the effect of rituximab on the results of post-therapy or follow-up PET scans was not one of the aims of this study.

PET scans can detect metabolic changes which precede changes in tumor size; this enables to assess response earlier during treatment.⁵² While end of therapy PET/CT in FDG-avid aggressive NHL such as DLBCL is a good predictor of outcome, the role of interim PET/CT is still controversial because of its low PPV.²² Clinical trials study the prognostic role of interim PET/CT aiming at optimizing outcomes and reducing toxicity i.e. response-adapted therapy.⁵³ Interim PET/CT is usually performed after 2 - 4 cycles of the standard 6 cycles chemotherapy to identify patients who could benefit from earlier change in treatment.⁵⁴ Still the role of interim PET/CT remains unclear, where some studies found that a negative interim PET/CT is associated with a better ORS and DFS.¹³ On the other hand, other studies have not reported similar outcomes; partly due to use of different methods for analyzing the PET/CT scans.^{15,23,24} Currently, changing treatment based on interim PET/CT result is not recommended unless disease progression is detected.²³ Among the methods to improve the PPV of interim PET is the use of quantitative approaches like the reduction of the maximum SUV in the 'hottest' lesion before and during treatment, known as Δ SUV.^{55,56} In this trial interim PET/CT was not done because of the high cost and limited finances. To date, the role of CT in lymphoma has been limited to assessing disease sites in combination with PET.

Following first line therapy of lymphoma around 30-50% of advanced HL and DLBCL relapse despite the improvements in survival rates.⁵⁷⁻⁵⁹ Monitoring of lymphoma patients who achieved remission depends on clinical symptoms and signs for the earliest indication of recurrent disease in up to 80% of presentations.⁶⁰ Surveillance imaging is still widely done using CT scans when necessary.⁶¹ Follow-up PET/CT scans in patients who are in remission have high false-positive rates⁶² and are not generally recommended. The PPV for surveillance PET scans range from 21% to 74% for aggressive NHL.^{51,63-65} False positive scans can lead to unnecessary biopsies and patient anxiety. In a meta-analysis by Terasawa *et al.*⁴¹ the authors demonstrated that the sensitivity and specificity of PET in detecting relapse for HL were 50 - 100 and 67 - 100% respectively, while for NHL 33 - 77 and 82 - 100%,

respectively regardless of a residual mass on CT. The low PPV associated with surveillance PET scans limits their clinical benefit in detecting patients who would benefit from more treatment.^{66,67} Han *et al.*⁵⁰ observed a low PPV 19% in follow-up PETs of 38/48 DLBCL patients treated with R-CHOP. El-Galaly *et al.*⁶⁴ studied 52 patients with aggressive NHL, including 43 patients with DLBCL in whom PPV of surveillance NHL was 21%. The Lugano criteria recommend CT imaging for follow-up as indicated by clinical signs and/or symptoms. We followed the majority of patients in this study using CT scans, PET/CT was performed in only 9/30 patients which was negative in 8/9 of these patients. The high false positive rate of surveillance PET scans indicates the need for more refinement of the interpretation criteria. CT had a similar low PPV 29% but at lower cost than PET/CT.⁶³ However, in some selected relapsed cases PET/CT can be justified.^{64, 65}

Prognosis of patients with negative post-treatment PET/CT is excellent compared to a positive scan. Saepen *et al.*¹⁴ showed that 56 out of 67 NHL patients had a negative post-therapy PET/CT and remained in complete remission at a median duration of 1.7 years, whereas all 26 with positive PET/CT relapsed at a median of 2.4 months. In our study 22 out of 30 patients had a negative end of treatment PET/CT, where 13 patients remained in remission for the whole follow-up duration and 9 patients relapsed after a median DFS of 12 months. As regards the factors affecting the result of end of therapy PET/CT, our findings confirmed the known prognostic factors of aggressive NHL affecting PET result and hence DFS, although not all reached statistical significance. In this study nodal versus extranodal disease, presence or absence of B symptoms, type of chemotherapy and IPI score were statistically significant. Dabaja *et al.*⁴⁶ studied 300 patients diagnosed with DLBCL; they confirmed the correlation of the known prognostic factors with the outcome in patients with DLBCL including type of therapy, response to therapy, and IPI score. Also they emphasized the role of CT showing residual disease > 2 cm in PET/CT negative patients, and recommended biopsy or close follow-up of suspicious masses. Similarly, Abo-Sheisha and Abdel-Fattah⁴⁵ showed many factors which affected the PET/CT result including stage of the disease, bone marrow involvement, IPI score, performance status, residual mass > 1.5 cm ($p < 0.005$).

We acknowledge the shortcomings of our study. The retrospective nature of the study may lead to information bias, since some data may be missing, the subjectivity associated with reading PET scans, the very small number of patients and the short follow-up duration.

5. Conclusion

PET/CT scans have an established role in staging and assessment of response in aggressive NHL. In accordance with other studies we concluded that end-of-therapy PET/CT is a good predictor of DFS and ORS and helps to guide the need for further therapy. Relapsed patients had a significantly shorter DFS following a positive scan than after a negative scan. CT continues to have an important role in post-treatment response assessment whether as a single modality or in combination with PET scan. In Egypt, CT scan is more widely available for post-treatment response evaluation of aggressive NHL and at lower cost. Ideally, the result of the PET/CT scans should be interpreted in a multidisciplinary setting depending on the clinical situation and the expected prognosis of the disease.

Conflict of Interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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