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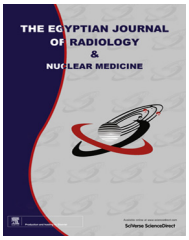

ORIGINAL ARTICLE

Prognostic evaluation of PET/CT in residual post-chemotherapy masses in patients with diffuse large B-cell lymphoma and its impact on survival

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KEYWORDS

PET/CT;
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Abstract *Aim of the work:* To evaluate the prognostic value and accuracy of PET/CT in DLBCL patients with post-treatment CT-residual masses with concern in overall (OAS) and progression-free survival (PFS).
Materials and methods: We retrospectively studied 62 patients with DLBCL who had CT documented residual masses (CRu) after completion of chemotherapy.
Results: Forty-four patients with negative PET scan were free of relapse while 4 out of 18 patients with positive scan showed CR, the other 14 patients had developed relapse. PET attained a sensitivity of 100%, a specificity of 91%, a NPV of 100% and a PPV of 77.8% and an accuracy of 93.5%. The median OAS time was 33.59 months in patients with negative scan and 19.00 months in patients with positive scan with highly significant correlation (*P* value 0.0001) and the median PFS time was 29.53 months in patients with negative scan versus only 4.00 months in patients with positive scan with highly significant correlation (*P* value 0.0000).
Conclusion: PET/CT plays helpful part in evaluation of therapy response in DLBCL patients with CT residual mass and post-chemotherapy PET could be used as an accurate and good predictor of OAS and PFS.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequent type of non-Hodgkin's lymphoma (NHL). Its outcome is heterogeneous, with some patients being cured but others not responding to therapy and eventually dying as a result of the disease (1). Although many patients initially respond to R-CHOP chemotherapy (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone), the 5-year overall survival (OS) rates for patients with DLBCL vary from 45% to 82% reflecting the heterogeneous nature of this disease (2).

Abbreviations: PET/CT, positron emission tomography/computed tomography; CRu, complete remission/unconfirmed; DLBCL, diffuse large B-cell lymphoma; OAS, overall survival; PFS, progression-free survival; CR, complete remission; SUV, standard uptake value; LDH, lactate dehydrogenase hormone

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Positron emission tomography (PET) with (18) F-FDG is an important noninvasive diagnostic tool for management of patients with lymphoma and most clinical investigators are convinced that its use will have an impact on the National Comprehensive Cancer Network (NCCN) guideline recommendations (3).

PET-CT is the standard imaging modality for staging and determining remission status at the conclusion of therapy for the aggressive lymphomas. It is clearly superior to CT alone when attempting to identify active disease after therapy completion. In addition, PET-CT has led to the revision of response criteria, allowing the elimination of the complete remission/unconfirmed category (4).

In the diagnosis of DLBCL, 18-fluorodeoxyglucose positron emission tomography (18-FDG-PET/CT) has proved to be highly sensitive in determining sites of disease (3) but the residual lymph node mass was a commonly encountered diagnostic challenge because it is difficult at CT to differentiate post treatment fibrosis from residual viable malignant changes. PET/CT has been found useful in the assessment of therapeutic response because of its improved utility in discriminating benign fibrosis (low-grade or absent FDG uptake) and residual active lymphoma (elevated FDG uptake) (5).

In the case of patients with PET/CT findings of residual disease, a clinical decision is required that may involve continuing therapy, switching therapy, or consideration of stem cell transplantation. In addition, residual FDG positivity at the end of therapy is predictive for survival (6).

The aim of this study is: to evaluate the prognostic value and accuracy of PET/CT in DLBCL patients with post-treatment CT-residual masses with concern in overall and progression-free survival (PFS).

2. Materials and methods

2.1. Patients

We retrospectively reviewed the records of 85 patients with pathologically confirmed DLBCL according to WHO classification for Tumors of Hematopoietic and Lymphoid Tissue (7). They were treated and followed up in the Clinical Oncology Department of the Tanta University Hospital during the period from April 2010 to October 2013. Twenty-three patients were excluded from our study because they had received radiotherapy after chemotherapy because previous analysis of other population showed that radiation given after chemotherapy had a significant effect on OAS and PFS for patients who achieved CR after chemotherapy (8) also there was other exclusion like pregnancy and diabetes.

So, our study included 62 eligible adult patients aged $\geqslant$18 years and had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2 (9). Staging of lymphoma was done according to the Ann Arbor staging system: Stage I (Involvement of a single lymph node region), Stage II (Involvement of two or more lymph node regions or lymphatic structures on the same side of the diaphragm), Stage III (Involvement of lymph node regions on both sides of the diaphragm), Stage IV (Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues) (10) and risk factor evaluation was done according to International non-Hodgkin's Lymphoma Prognostic Factors Project (IPI) (11), the risk factors being age greater than 60 years, Stage III or IV disease, Elevated serum LDH, performance status of 2, 3, or 4, and more than 1 extranodal site.

All patients had finished chemotherapy and showed CT evidence of residual mass >1.5 cm. Written; informed consent was obtained from all patients before enrollment into the study.

2.2. Treatment

All patients were treated with six cycles of R-CHOP regimen [rituximab 375 mg/m^{2}i.v. on day one D1, cyclophosphamide 750 mg/m^{2}i.v. on D1, vincristine 1.4 mg/m^{2}i.v. on D1, doxorubicin 50 mg/m^{2}i.v. on D1, and prednisone 100 mg p.o. on D1–5] recycled every 21 days. Complete hematological work up was done before every cycle. All the investigations done during the pretreatment period were repeated by the end of the 3rd cycle and properly assessed. The response to treatment was assessed according to international workshop criteria (REF) (12), complete remission (CR) was defined as disappearance of all evidence of disease. Relapse disease or progressive disease was defined as any new lesion occurring or a lymph node/extranodal site with a short axis diameter of <1.0 cm increasing by $\geqslant$50% and to a size of 1.5×1.5 cm or more than 1.5 cm in the long axis and at least a 50% increase in the longest diameter of any single previously identified node/extranodal site >1 cm in its short axis.

2.3. Follow up

Patients were seen weekly during treatment and then monthly in the first year, every 2 months in the second year, every 4–6 months thereafter or at any time if there is any complaint. Patients were monitored by physical examination, complete hematological work up, chest X-ray, abdomino-pelvic ultrasonography, computed tomography of the neck; chest, abdomen and pelvis were done at the end of treatment, every 3 months in the 1st year, every 6 months in 2nd year and annually thereafter and in any time when clinically indicated (12). The follow up period ranged between 6 months to 36 months with a median of 14 months. Fourteen patients with progressive disease (with evidence of relapse) were shifted to salvage therapy.

2.4. Methods

2.4.1. PET/CT

All patients were imaged with dedicated PET-CT scanner (Siemens, Biograph-2) 6–8 weeks after completion of chemotherapy. All patients were fasted for at least 6 h before FDG injection. Fasting blood glucose level of less than 150 mg/dl was requirement in all patients. The scan started 60 min after intravenous administration of 2.516 MBq (0.068 mCi/kg) FDG, during this period, the patient was instructed to rest without talking. CT was performed from skull base to pelvis by performing a scout view followed by a spiral CT with 80 mA, 140 kVp. No oral contrast was given, and water only was used to delineate bowel. Intravenous 130 ml of iohexol (Omnipaque 300 mg iodine/ml) was administered. On completion of CT, 2D PET emission data (4 min per bed position covering an axial FOV of 15.7 cm with a 3-slice overlap) was obtained. The total scanning time varied between

25 and 30 min for every patient. The CT, PET and PET/CT images were reconstructed in trans-axial, coronal and sagittal planes.

2.5. Image analysis

According to the criteria of the International Harmonization Project (13), visual assessment was used to categorize FDG-PET scan findings as positive or negative. A PET/CT scan is defined as positive if there is abnormal FDG uptake greater than background in surrounding tissue and unrelated to physiologic sites of tracer uptake (e.g. bowel, myocardium), without a specific standardized uptake value (SUV) cut-off and a PET/CT scan is defined as negative if there is no 18F-FDG uptake. For residual hepatic or splenic lesion, abnormal uptake was defined as FDG accumulation greater than in the liver (13).

2.6. Statistical analysis

The data were analyzed using SPSS 13.0 software package. The correlation of PET/CT negative residual masses and PET/CT positive residual masses with different patients' characteristics was analyzed using Chi-square test. Progression-free survival was defined as the length of time from remission to being worse and overall survival was defined as the length of time from diagnosis to death. The Kaplan–Meier method and Log-rank test were used to analyze the correlation of patient survival with PET/CT negative residual masses and PET/CT positive residual masses; a significant level of P value (0.0001) was used. Sensitivity, specificity, accuracy, positive (PPV) and negative predictive values (NPV) of positive and negative PET scan were calculated.

3. Results

Between April 2010 and October 2013, the total number of patients eligible for this study was 62. Patient and tumor characteristics are listed in Table 1. The age ranged from 18 to 73 years and the mean age was 51.146 and 52.357 years in negative and positive PET/CT patients respectively with no significant differences found between them (P value 0.760). About 81% of patients with negative PET/CT had PS (0–1) versus only 42.85% patients with positive scan with statistically significant differences (P value 0.017). About 62% of patients were males. According to stage of disease,

Table 1 Patient characteristics according to PET status.

		PET							
		PET/CT (−ve)		PET/CT (+ve)		Total		Chi-square	
		N	N%	*N*	%	*N*	%	X2	*P*-value
PS	0	13	27.08	1	7.14	14	22.58	8.131	0.017
	1	26	54.17	5	35.71	31	50.00		
	2	9	18.75	8	57.14	17	27.42		
Sex	Female	18	37.50	6	42.86	24	38.71	0.131	0.717
	Male	30	62.50	8	57.14	38	61.29		
Bsymtoms	Negative	31	64.58	5	35.71	36	58.06	3.710	0.054
	Positive	17	35.42	9	64.29	26	41.94		
Stage	I	18	37.50	1	7.14	19	30.65	19.121	0.000
	II	22	45.83	2	14.29	24	38.71		
	III	4	8.33	4	28.57	8	12.90		
	IV	4	8.33	7	50.00	11	17.74		
Extranodal	Negative	40	83.33	14	100.00	54	87.10	4.429	0.035
	Positive	8	16.67	0	0.00	8	12.90		
Size 7	< 7 cm	39	81.25	12	85.71	51	82.26	0.154	0.695
	> 7 cm	9	18.75	2	14.29	11	17.74		
Bmarrow	Normal	46	95.83	8	57.14	54	87.10	11.934	0.001
	Hyper	2	4.17	6	42.86	8	12.90		
LDH	Normal	25	52.08	4	28.57	29	46.77	2.407	0.121
	High	23	47.92	10	71.43	33	53.23		
Size of res	< 2	41	85.42	5	35.71	46	74.19	12.678	0.000
	> 2	7	14.58	9	64.29	16	25.81		
Nu of resid	1	35	72.92	4	28.57	39	62.90	10.762	0.005
	2	10	20.83	5	35.71	15	24.19		
	3	3	6.25	5	35.71	8	12.90		
IPI	0	12	25.00	0	0.00	12	19.35	26.773	0.000
	1	24	50.00	1	7.14	25	40.32		
	2	9	18.75	5	35.71	14	22.58		
	3	2	4.17	6	42.86	8	12.90		
	4	1	2.08	2	14.29	3	4.84		
Events of OAS	Alive	44	91.67	9	64.29	53	85.48	5.578	0.018
	Died	4	8.33	5	35.71	9	14.52		

−ve, negative; +ve, positive; PS, performance state; B marrow, bone marrow; LDH, lactate dehydrogenase hormone; nu of resid, number of residual; IPI, international prognostic index; OAS, overall survival.

Table 2 The clinical course and PET findings in 62 patients with residual mass.

PET/CT		CR	Relapse	Total
Negative	*N*	44	0	44
	%	70.97	0.00	70.97
Positive	*N*	4	14	18
	%	6.45	22.58	29.03
Total	*N*	48	14	62
	%	77.42	22.58	100.00
Sens.	Spec.	PPV	NPV	Accuracy
100.000	91.667	77.778	100.000	93.548

Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; CR, complete remission.

the majority of negative PET/CT patients were with early stages (I and II) with highly significant difference (*P* value 0.000).There were no significant differences found between negative PET/CT, positive PET/CT patients and bulky ($\geqslant$7 cm in diameter) and non bulky disease (*P* value 0.695). The majority of patients with negative scan had low risk IPI, while the remainder had an IPI score of >2 with highly significant correlation (*P* value 0.000). Bone marrow involvement was detected in 42.86% of patients with positive scan compared to only 4.17% of patients with negative scan (*P* value), as regards LDH, there was no significant difference between either negative PET/CT or positive PET/CT patients and the level of this hormone (*P* value 0.121).

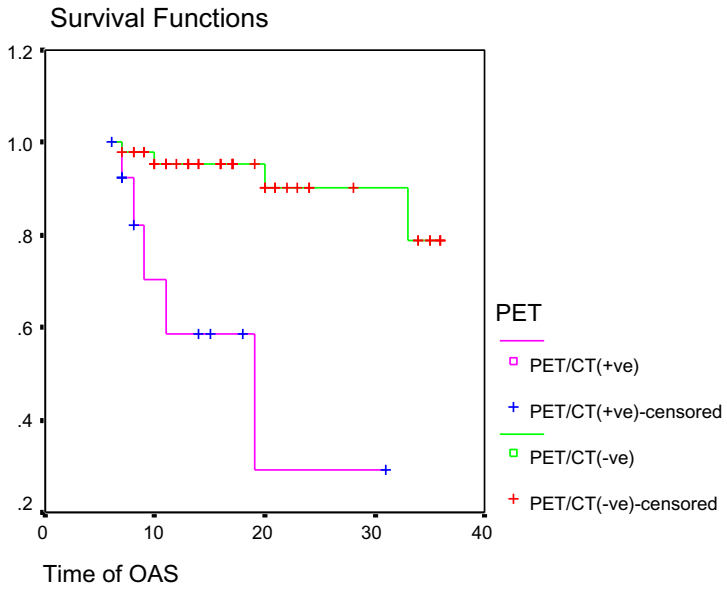

Fig. 1 Kaplan-Meier plot of overall survival (OAS) curves for (18) patients with PET-positive residual masses compared with (44) patients with PET-negative residual masses.

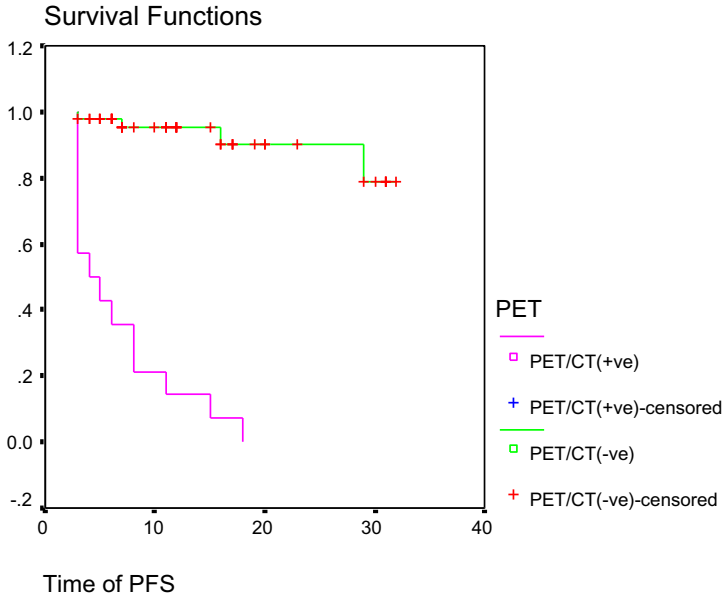

Fig. 2 Kaplan-Meier plot of the progression-free survival (PFS) curves for (18) patients with PET-positive residual masses compared with (44) patients with PET-negative residual masses.

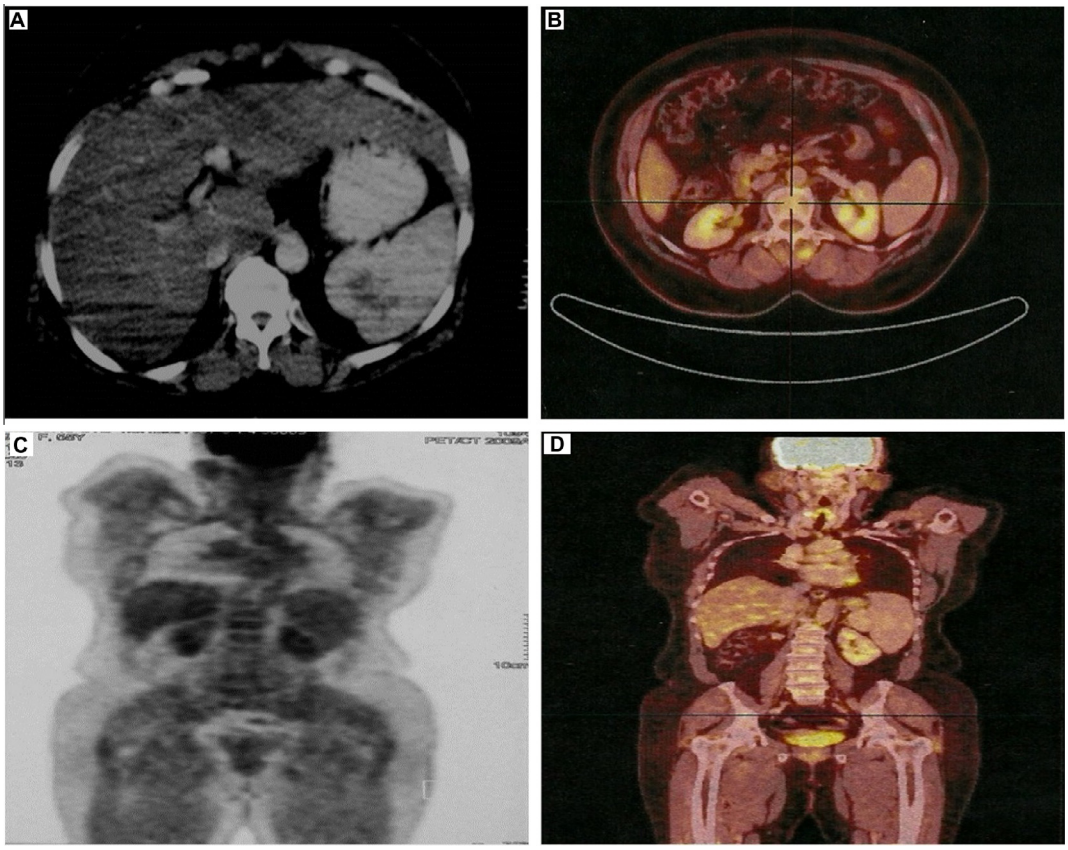

Fig. 3 A female patient aged 55 years with stage I-DLBCL referred for a routine follow up 6 months after completion of her chemotherapy, no clinical symptoms, post-treatment CT showed splenic lesion. (A) Axial CT scan with contrast shows: a hypodense focal lesion in the spleen measured 2.5 cm. (B–D) Maximum–intensity projection PET/CT images (axial and coronal) shows no uptake could be detected in the lesion (negative PET/CT scan) indicating fibrosis and the patient showed continuous CR in the next follow up.

In terms of the number of residual sites, the majority had single residual site (39 patients), 15 patients had 2 residual sites and only 8 had 3 residual sites. PET scan was negative in 72% of patients with single residual mass (*P* value 0.005).

As regards the clinical course of patients with negative and positive PET/CT scan, the total 44 patients with negative PET scan were free of relapse and showed sustained CR during the follow up period while 4 out of 18 patients with positive scan showed sustained CR which was considered as false positive result. The other 14 patients with a positive PET scan had developed relapse either in the same or outside the residual site.

In 62 patients with residual masses PET attained a sensitivity of 100%, a specificity of 91%, a NPV of 100% and a PPV of 77.8% and an accuracy of 93.5% in the prediction of relapse (Table 2).

During follow up period, 53 patients remained alive and the median OAS of all patients was 31.27 months, the majority showed negative PET scan with significant difference (*P* value 0.018). In our study, the median OAS time was 33.59 months in patients with negative scan and 19.00 months in patients with positive scan with highly significant difference (*P* value 0.0001) Fig. 1, while the median PFS time was 29.53 in patients with negative scan versus only 4.00 months in patients with positive scan with highly significant difference (*P* value 0.0000) Figs. 2–5.

4. Discussion

The lymphomas are a heterogeneous group of diseases with respect to their biology, treatment, and prognosis. Despite the high rate of cure of Hodgkin lymphoma (HL) and diffuse large B-cell lymphoma (DLBCL), there is a need to alter therapy in patients unlikely to benefit from standard treatment, while reducing treatment intensity in patients with low risk disease (14). Positron emission tomography (PET) using F-18-fluorodeoxyglucose (FDG), integrated with computed tomography (CT) (PET/CT) has become widely used in the staging and evaluation of therapy response in lymphomas, and may provide the means for such an individualized approach (15).

In this study, we investigated the role of PET/CT scan in 62 patients with DLBCL and showed CT-residual masses after chemotherapy. The most important result in this study was: the majority 44 out of 48 patients with negative PET scan were free of relapse and showed sustained CR during the follow up period, while 4 out of 18 patients with positive scan showed sustained CR which was considered as false positive result. The other 14 patients with a positive PET scan had developed relapse with follow up in the range of 18 months, either in the same or outside the residual site. So, in 62 patients with residual masses PET attained a sensitivity of 100%, a specificity of

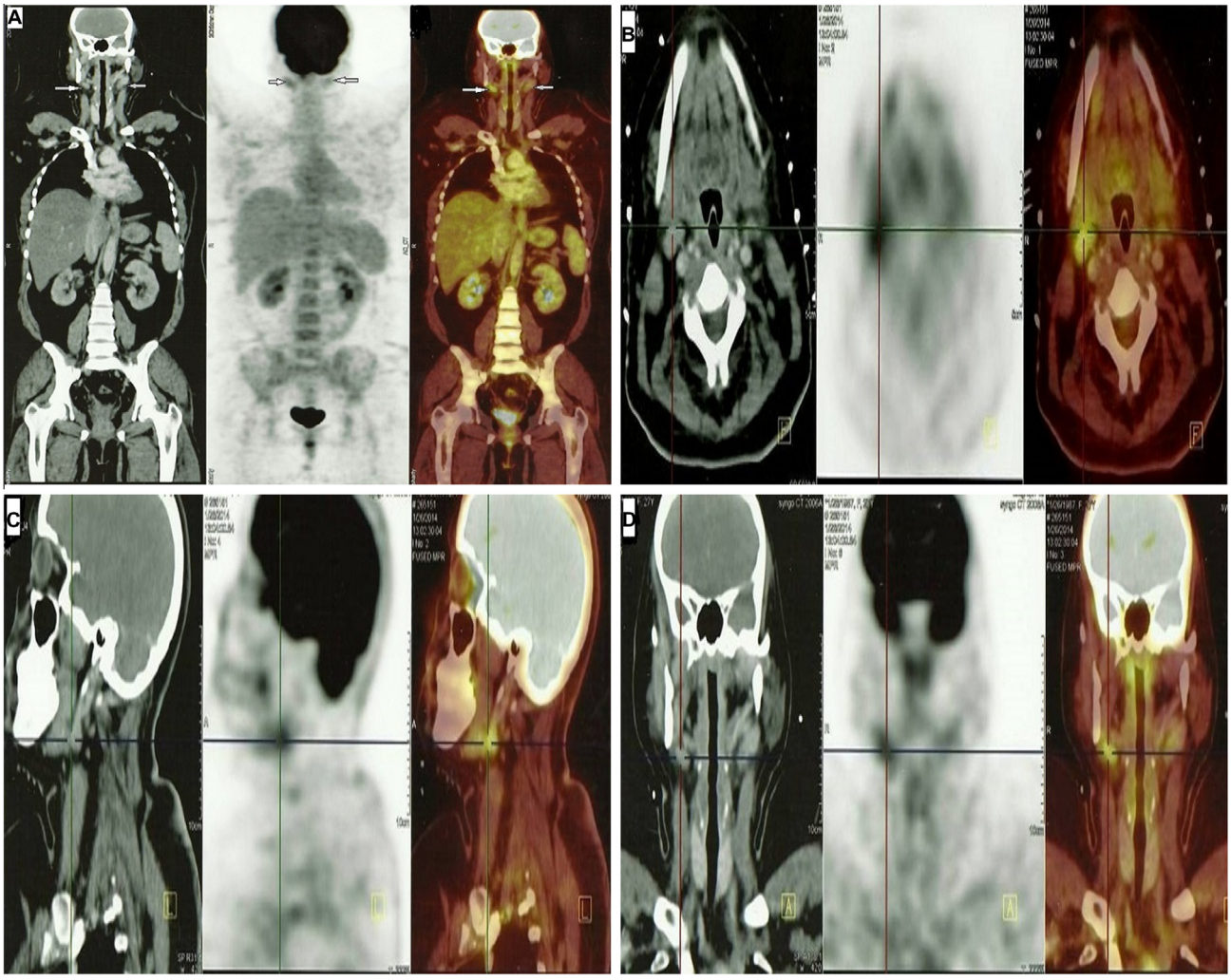

Fig. 4 A female patient aged 27 years with stage II-DLBCL, 1 year after chemotherapy presented clinically by bilateral enlarged 2 cervical lymph nodes, post-treatment CT shows: the right sided lymph node (right arrow) is 1.7 cm and the other one (left arrow) is smaller in size. (A) Coronal whole body fused PET/CT images showed: active uptake of FDG in the right lymph node with maximum SUV ~ 5.6, no uptake of the left sided lymph node indicating fibrosis. (B) Axial & (C) Sagittal and (D) Coronal fused PET/CT images show: abnormal activity of the right sided lymph node.

91%, a NPV of 100% and a PPV of 77.8% and an accuracy of 93.5% in the prediction of relapse.

Terasawa et al. (16) in 19 studies included 254 patients with aggressive NHL, they reported ranges for the sensitivity and specificity of PET/CT in predicting disease relapse which were 50–70% and 67–100%, respectively. Zijlstra et al. (17) included 15 studies, involving 705 patients, all patients were for post-treatment evaluation and residual masses, their sensitivity and specificity for detection of residual disease in non-Hodgkin's lymphoma, were 72% and 100%, respectively, these results disagree with our study as PET showed high sensitivity (100%) and specificity (92%) in prediction of disease recurrence but our results agree with Lavely et al. (18) who studied 20 patients with non-Hodking's lymphoma after completion of therapy and they found that FDG-PET prediction of relapse had sensitivity of 100% and a specificity of 84%. Reske et al. (19) reviewed 15 other studies on differentiation of viable lymphoma from scar tissue in 723 patients. Their sensitivity for detection of active disease and recurrence was 100%.

Perhaps the clearest role for the use of PET in lymphoma is in post-treatment response assessment because of its ability to distinguish fibrosis or sclerosis from residual active disease. Many studies have demonstrated a role for post-therapy FDG-PET imaging in the prediction of aggressive NHL or HL recurrence (20).

A negative (NPV) (the ability of a negative PET scan to exclude persistent disease or future relapse) and a positive predictive value (PPV) (the ability of a positive PET scan to predict persistent disease or future relapse) of 80 and 100% were reported for FDG-PET in the identification of residual aggressive NHL after completion of first-line chemotherapy (21).

Juweid et al. (22) found in a retrospective evaluation of 54 patients with aggressive NHL, a PPV of 74% and a NPV of 100% for PET scans. Our results agree with those of Juweid et al. where our PPV was 78% and NPV was 100%.

We found that, patients with residual mass on CT and having a positive PET scan after finishing chemotherapy for

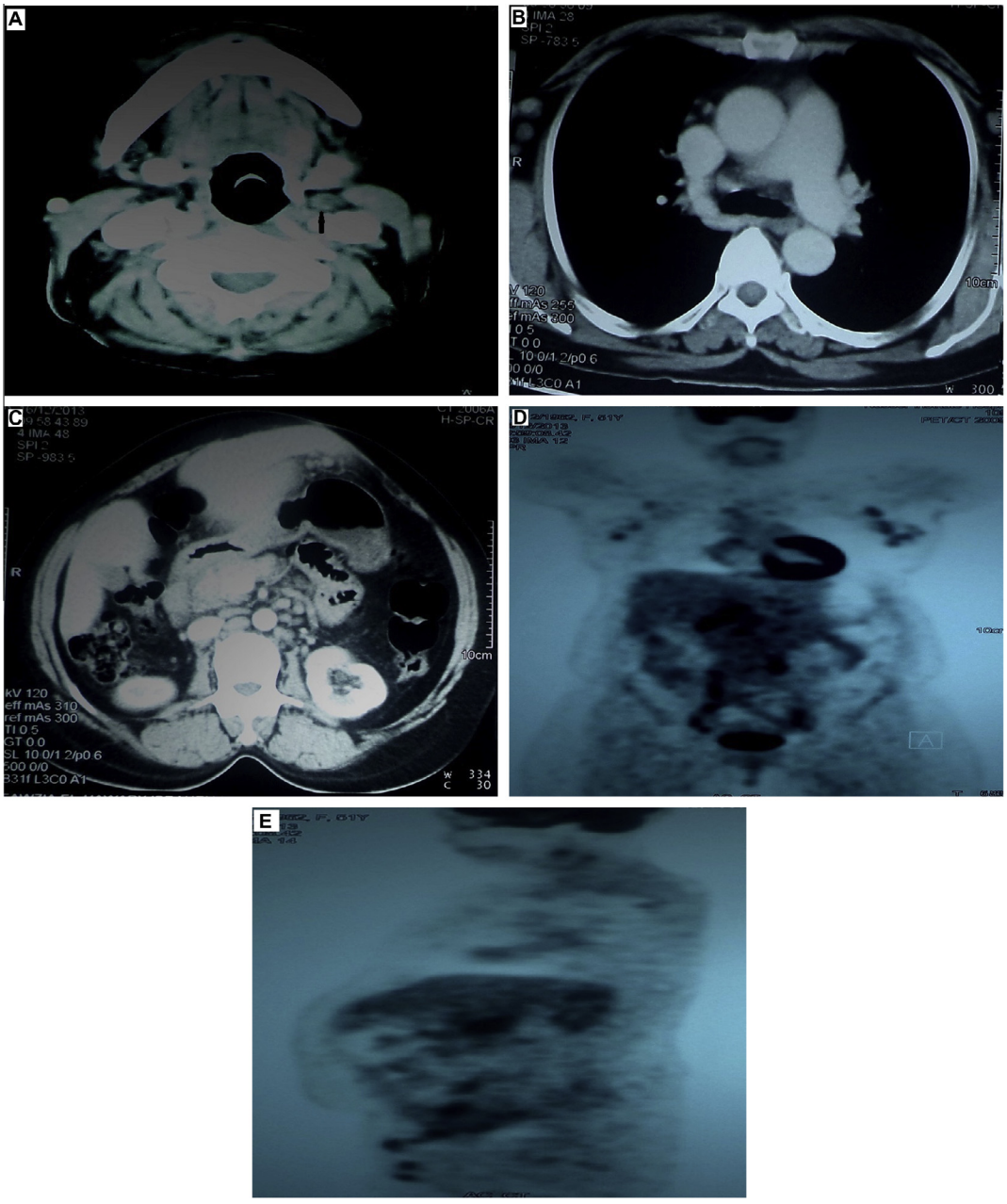

Fig. 5 A female patient aged 51 years with stage III-DLBCL, 4 months after chemotherapy, post-treatment CT shows: enlarged cervical, multiple small paraortic, axillary and abdominal lymph nodes. (A) Axial post–contrast CT scan of the neck shows: enlarged left deep cervical lymph node (black arrow). (B) Axial post-contrast CT scan of the chest shows: small para-aortic and multiple axillary lymph nodes. (C) Axial post-contrast CT scan of the abdomen shows: multiple enlarged abdominal lymph nodes. (D) & (E) Maximum–intensity projection PET/CT images (axial and coronal) shows: Bilateral cervical lymph nodes with maximum SUV ~ 4.4, right para-tracheal and retrocaval lymph nodes with maximum SUV ~ 5.6, multiple bilateral axillary lymph nodes measuring up to 3.5 cm with maximum SUV ~ 11.7, multiple enlarged abdominal lymph nodes; celiac, porta hepatis, para-aortic, mesenteric, bilateral common iliac, external and internal iliac as well as bilateral inguinal lymph nodes with maximum SUV ~ 11.6.

DLBCL may be significant in predicting OAS and PFS. DLBCL patients with a positive PET study in the residual mass had a poorer prognosis (14/18 recurrences) than patients with a negative PET study (no recurrence), the results of the Kaplan–Meier analysis of the progression-free survival (PFS) were significantly different with regard to these two groups (*P* value 0.0001). The median follow-up of the patients with positive PET/CT scan was 52.35 months (range 22 ± 73 months) and the median follow-up of the patients with negative PET/CT scan was 51.14 months (range 18 ± 70 months).

In terms of response, the 5-year OAS and PFS, Depaja et al. (23) in his study which included 300 patients with DLBCL, the rates for patients who achieved CR by PET scan were significantly higher than the rates for those who did not achieve a CR (i.e., showed relapse (*P* value 0.0001)). We found that OAS and PFS were significantly poorer in patients with

positive scan than patients with negative scan, the median PFS time was 29.53 months in patients with negative scan and only 4.00 months in patients with positive scan with highly significant correlation (*P* value 0.0000).

In the study by Depaja et al. (23), they found that several known prognostic factors correlate with outcome in patients with DLBCL, including response to therapy, type of therapy and IPI score. They stated that any residual disease larger than 2 cm on CT after therapy should be regarded with suspicion and such masses should be either subjected to biopsy or followed closely over time. If residual disease is present at more than one site, the suspicion for aggressive disease increased.

In our results, we found many factors affecting the result of PET scan, including stage of the disease, bone marrow involvement, IPI score, performance state, and size of the residual mass which was more than 1.5 cm (10), there was a significant correlation between these factors and the results of PET scan (*P* value 0.005).

This study has some limitations, 1st: it was a retrospective study, 2nd: small number of patients, 3rd: our treatment regimen was R-CHOP chemotherapy and other treatment like radiotherapy was not analyzed.

5. Conclusion

PET/CT plays helpful part in evaluation of therapy response in DLBCL patients with CT residual mass and post-chemotherapy PET could be used as an accurate and good predictor of OAS and PFS.

Conflict of interest

We have no conflict of interest to declare.

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