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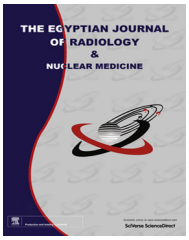

ORIGINAL ARTICLE

PET/CT in initial staging and therapy response assessment of early mediastinal lymphoma

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KEYWORDS

PET/CT;
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Mediastinum;
Therapy response

Abstract *Objective:* To detect accuracy of PET/CT in the initial staging, response after the first line and end of treatment in early mediastinal lymphoma patients compared to contrast CT.
Materials and methods: We studied 50 patients with pathologically proven lymphoma with a mean age = 27.5. All patients were at early stage. All patients performed CT and PET/CT for initial staging, after the first course of chemotherapy (after 4–6 weeks) and at the end of treatment (after 2–4 months).
Results: PET/CT upstaged 5 cases. At first line of treatment, PET/CT and CECT were agreeable in 32% of cases. PET/CT showed 100% sensitivity, 96.7% specificity, 95% positive predictive value and 100% negative predictive value. At the end of treatment both methods showed a 46% agreement. PET/CT was statistically significant in the follow up of hilar and axillary lymph nodes. PET/CT showed 100% sensitivity and specificity; compared to 62.5% sensitivity and 97.6% specificity for CECT in detection of extra-nodal disease sites.
Conclusion: PET/CT proved higher sensitivity and specificity over CECT. The major strength of PET/CT over CECT was its higher ability for detection of extra-nodal sites of lymphoma and excluding active disease in residual nodal mass lesions on follow up.

1. Introduction

Lymphoma is the most common primary hematopoietic malignancy (1). Lymphoma comprises a histological heterogeneous group of cancers derived from the cells of the immune system. The hallmark of the disease is the enlargement and proliferation of lymph nodes or secondary lymphoid tissues. Both NHL and Hodgkin's disease may also arise from or involve

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almost any organ of the human body (2). Intrathoracic disease is observed in about 70–85% of Hodgkin's disease patients and in 25–50% of those with Non Hodgkin's lymphoma (3). In early stage HL more than 90% are cured however they have a reduced life expectancy from long term adverse events. These include heart and lung disease and secondary malignancy (4). Risk adapted therapy by reducing the cycles of chemotherapy or omitting radiotherapy according to mid-treatment PET/CT is still under trial (5).

FDG PET has been widely used for staging of disease, detection of recurrence, and monitoring of treatment response in patients with Hodgkin's disease and NHL. In the past, the imaging evaluation and follow-up of lymphoma patients were based solely on findings at contrast-enhanced CT. However, contrast-enhanced CT has limited sensitivity in detecting lymphomatous involvement of normal-sized lymph nodes, bone marrow, spleen, and extra-nodal tissues (6,7). 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 studies show a high sensitivity for tumor detection and add important functional information to the inherent anatomic data provided with CT. PET/CT scanning allows the investigator to visualize and measure the intensity of residual metabolic activity within a lesion as well as estimating its size (6). Hodgkin's lymphoma is FDG avid, and PET/CT is a more accurate initial staging examination than conventional diagnostic CT, particularly for the detection of unexpected sites of extranodal lymphoma (7).

In a recent systematic review, the overall sensitivity and specificity of FDG PET/CT for initial staging of NHL and Hodgkin's disease were 97% and 100%, respectively (8). There is already a considerable literature on the use of FDG-PET and FDG-PET/CT in primary staging of lymphoma (9,10). However limited literature on the use of FDG-PET/CT evaluating the response to first line of treatment and follow up after the end to treatment was found, especially in cases of early stage mediastinal lymphoma.

Our aim was to show the accuracy and contribution of PET/CT in the initial staging, response after the first line of treatment and at the end of treatment in early mediastinal lymphoma patients in comparison to contrast enhanced CT (CECT) study.

2. Materials and methods

We studied 50 patients with pathologically proven lymphoma from April 2011 to July 2013. Their ages ranged from 2 up to 80 years (mean age = 27.5), including 25 males and 25 females. Exclusion criteria were diabetes mellitus and pregnancy. All patients were at early stage according to the CT findings. Histopathological diagnosis of lymphoma was established in all cases after biopsy whether surgical or image guided. None of the cases received any previous oncological treatment.

The following clinical data were obtained from all patients: sex, age, clinical stage, extranodal involvement, presence of B symptoms, bulky disease (tumor >10 cm and/or mediastinal bulk $>1/3$ of thoracic diameter), histologic subtype according to the WHO classification, albumin, and erythrocyte sedimentation rate (ESR), hemoglobin, leukocyte count and lymphocyte count.

All patients included in the study performed CT and PET/CT for initial staging, after the first course of chemotherapy (after 4–6 weeks) and after the end of treatment (after 2–4 months).

Staging was defined according to the Ann Arbor staging system. Treatment of early-stage disease was given according to the Nordic Lymphoma Group protocols (11). The first line of treatment was ABVD (adrifmycin, bleomycin, vinblastine, dacarbazine) in standard doses every 2 weeks (one cycle = 4 weeks) with dose modification, granulocyte stimulation, or delays depending on blood counts with or without local radiotherapy. Response of treatment was assessed according to the International Harmonization Project Criteria for Assessment of Response to Therapy for Lymphoma (12). The study was approved from the ethics committee in our University and informed written consents were taken.

3. Imaging protocol

FDG PET/CT scans were performed with integrated PET/CT scanners (Biograph 16, Siemens Medical Solutions, or Discovery 690, GE Healthcare, Waukesha, Wis). Blood glucose levels were recorded prior to FDG injection in all patients. Patients were instructed to fast for at least 6 h prior to the administration of FDG to decrease physiologic blood glucose levels and to reduce serum insulin levels to near baseline. Patients were not premedicated with muscle relaxants or sedated. 18F-FDG (0.21 mCi/kg of body weight [7.78 MBq/kg]) was injected intravenously 45–90 min prior to image acquisition, and patients were asked to void their urine immediately before the PET/CT scan. Oral contrast material was not administered.

Once patients were positioned in the scanner, 125 ml of iohexol (Omnipaque 240 or 300; GE Healthcare, Princeton, NJ) was injected intravenously at a flow rate of 4 mU/s. PET and low-dose CT images (20–120 mAs) in the whole body were obtained in an arms-up position with scanning times of approximately 20–30 min. In all patients, emission images were acquired for 3 min per bed position in a three-dimensional mode. The contrast material-enhanced CT data were used for attenuation correction of the PET emission data and also served as a diagnostic study. PET/CT, PET, and CT images were displayed and reconstructed in the transaxial, coronal, and sagittal planes.

4. Image analysis

All PET/CT images were analyzed at all stages. Analyses included measurements of the maximum anteroposterior and transverse dimensions of the mediastinal mass on axial CT images. A lesion was classified as positive on PET if there was focally increased FDG uptake above background that was not explained by physiological activity and measurements of maximum standardized uptake values of mediastinal mass (SUVmax). The SUVmax was defined as the highest activity concentration (in megabecquerels per milliliter) within the target tissue with respect to the injected dose per kilogram of body weight (in megabecquerels per milliliter per kilogram of body weight), as determined by using the standard software of the manufacturer. While in conventional CT, size

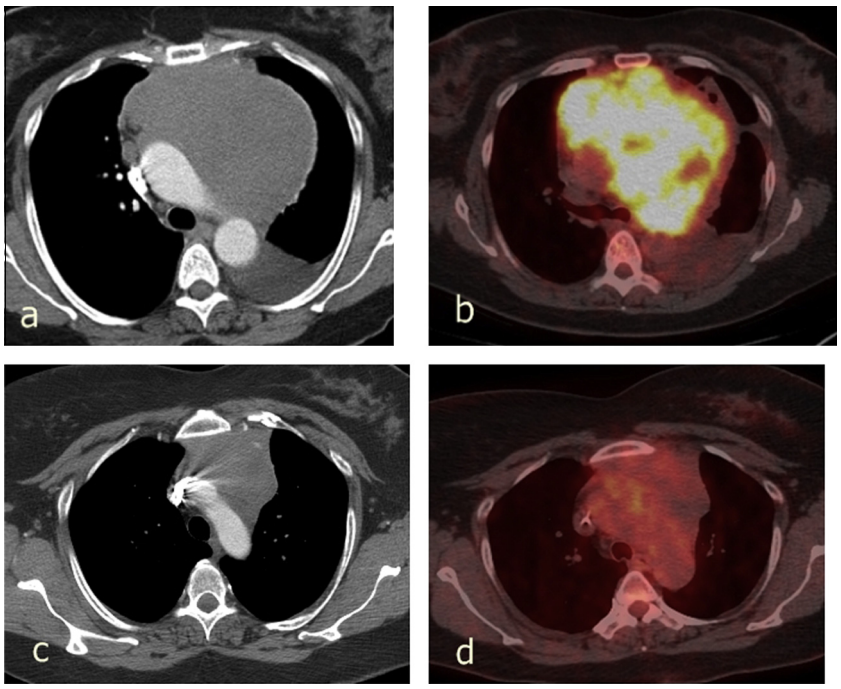

Fig. 1 A 12 year old male with pathologically proven HL presented a large anterior mediastinal soft tissue mass lesion (a); it shows FDG uptake in PET-CT with SUVmax 14.2 (b); 6 weeks after chemotherapy, the mass lesion shows partial regression in size on CT (c); yet with no detectable FDG uptake denoting full metabolic response to therapy on PET/CT (d).

measurements were the parameter used for comparison of the pre and post treatment scans. Extranodal thoracic (alveolar, chest wall, pleural and bone), hilar and axillary lymph node affection were also evaluated before and after therapy. The findings for each of these sites were graded as positive or negative for lymphomatous infiltration.

5. Statistical analysis

Data were statistically described in terms of range, mean ± standard deviation (±SD), median, frequencies (number of cases) and percentages when appropriate. Comparison of quantitative variables between the study groups was done using Kruskal–Wallis analysis of variance (ANOVA) test. For comparing categorical data, Chi square (χ^2) test was performed. Sensitivity, specificity, positive and negative predictive values, accuracy, *P* value were calculated to test validity of PET/CT. Exact test was used instead when the expected frequency is less than 5. *P* values less than 0.05 were considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

6. Results

The study included 50 patients with mediastinal lymphoma with 27.5 mean age.

Histopathologically; we had 37 cases of Hodgkin's lymphoma (74%), 12 cases of B-cell Non Hodgkin's lymphoma (24%) and 1 case of T-cell lymphoma (2%).

6.1. In the initial staging

CT depicted 34 cases in stage I, 13 cases in stage II and 3 cases in stage IIE. PET/CT depicted 31 cases in stage I, 2 cases in stage IE, 11 cases in stage II, 4 cases in stage IIE and 2 cases in stage IV. Thus, PET/CT disagreed with CT in the initial staging of 5 cases (10%). PET/CT upstaged 2 cases from stage I to IE, as it detected a single extra-nodal pleural site of disease and 1 case from stage II to IIE, with PET/CT adding the presence of a single chest wall lesion. Two cases were upstaged from stages I and II to stage IV. One of them presented with enlarged mediastinal lymph nodes (stage I) however, PET/CT was able to depict two areas of intense FDG uptake in the vertebra (SUVmax 11.7) and the anterior chest wall muscles (SUVmax 11.1). The other patient presented with enlarged mediastinal and hilar lymph nodes (stage II) yet the PET/CT depicted two pulmonary nodules (SUVmax 10.8) and a patchy area of alveolar infiltration (SUVmax 3) that was pathologically proven to be parenchymal lymphoma changing the case to stage IV.

According to size, seven patients had bulky mediastinal lesion >10 cm in size (Fig. 1).

6.2. After the first line of treatment (4–6 weeks)

Conventional CT revealed complete regression in only 7 cases (14%), partial regression in 31 cases (62%) and stationary course in 12 cases (24%). PET/CT revealed complete regression in 30 cases (60%), partial regression in 11 cases (22%), progression of the disease in 7 cases (14%), stationary course in one case (2%) and mixed response to treatment was detected in 1 case (2%) where increased metabolic

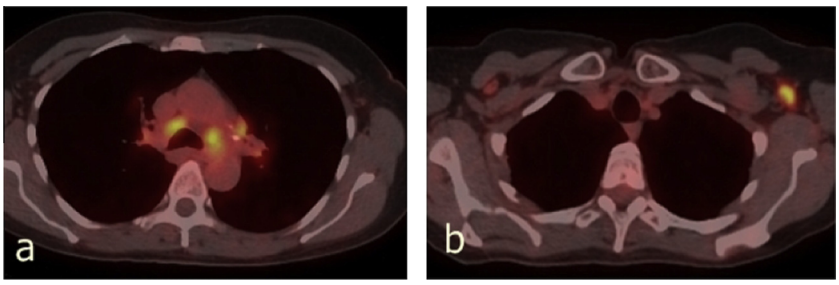

Fig. 2 PET/CT in a 60 year old female patient with HL showing multiple enlarged mediastinal lymph nodes (a) with hypermetabolic lymph nodes in both axillary regions (SUVmax = 4.6) (b), Biopsy was taken from the axillary lymph nodes and histology revealed reactive inflammatory cells denoting false positive result by PET-CT.

Table 1 Comparison between PET-CT and CT results in treatment response after the first course of chemotherapy.

Disease response in PET-CT		Disease response in CECT		
		Complete regression	Partial regression	Stationary
Complete regression	30	6	19	5
	60%	12%	38%	10%
Mixed response	1	0	1	0
	2%	0%	2%	0%
Partial regression	11	0	9	2
	22%	0%	18%	4%
Progressive	7	1	2	4
	14%	2%	4%	8%
Stationary	1	0	0	1
	2%	0%	0%	2%
Total	50	7	31	12
	100%	14%	62%	24%

SUVmax in bilateral hypermetabolic axillary lymph node was detected, the pathology-however- revealed reactive inflammatory tissue and it was assigned as a PET/CT false positive result (Fig. 2) (Table 1).

Both methods (PET/CT and CT) were agreeable in 32% of cases (12% of cases showing complete regression, 18% showing partial regression and 2% showing stationary course).

CECT was true positive in 18 cases, true negative in 6 cases, false positive in 25 cases and false negative in 1 case showing a 94.7% sensitivity, 19.4% specificity, 41.8% positive predictive value and 85.7% negative predictive value. PET/CT was true positive in 19 cases, true negative in 30 cases, false positive in 1 case and shows no false negative results with a 100% sensitivity, 96.7% specificity, 95% positive predictive value and 100% negative predictive value.

6.3. After the end of chemotherapy (2–4 months)

We divided the patients into two groups, group I represents patients with complete regression of the disease after the first course of chemotherapy (30 patients) and group II represents patients (20 patients) with partial regression, stationary or progressive disease course.

In group I: 29 cases (96.7%) continued to show complete metabolic regression on PET/CT, conventional CT agreed in 12 cases (40%), while in 8 cases (27%) it shows stationary size and in the other 9 cases (30%) it shows partial regression in size of the lesions. Only one case (3%) showed a newly developed small soft tissue extra-nodal lesion involving the pleura with SUVmax = 18.4 denoting disease relapse by PET/CT which was confirmed by biopsy and histopathology (Fig. 3). This case was misdiagnosed as stationary by CT. Both PET/CT and CT showed 40% agreement (Table 2).

In group II: 14 cases (70%) show complete regression with PET/CT, conventional CT agreed in only 6 cases (25%) while it shows 4 cases with partial regression (20%) and 4 other cases stationary (20%). Both CT and PET/CT agreed that two cases show partial regression (10%). 4 cases (20%) where stationary in PET/CT, CT agreed in 3 of them (15%) and showed partial regression in the last one (5%). Both methods agreed in 55% of the cases and disagreed in 45% of cases (Table 3).

Thus, in both groups the agreement was in only 23 cases representing 46%.

In general, the mean SUVmax estimated in the initial study in mediastinal lymphoma cases was 12, after the first course of chemotherapy, the median SUVmax was 3.1, at the end of treatment, the median SUVmax was 1.3.

In mediastinal HL specifically; the mean SUVmax was 11.3, 2.9 and 0.5 in the initial, first follow up and second follow up study respectively while, cases of mediastinal B cell NHL showed mean SUVmax of 14.2 in the initial study, 5.5 in the first follow up and 3 in the second follow up study.

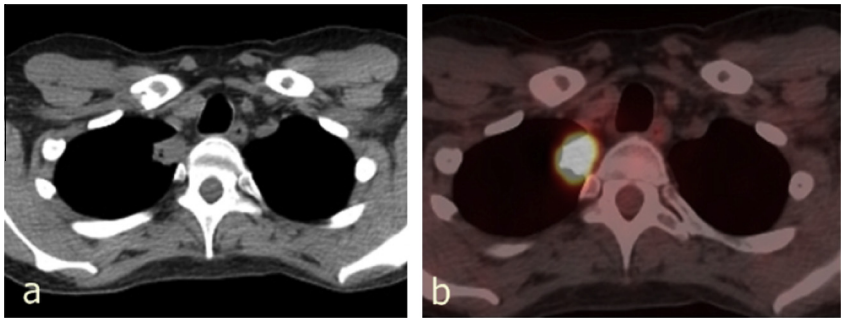

Fig. 3 A 26 year old female patient with NHL. CECT (a) shows a pleural nodule. PET-CT (b) shows a 4×3 cm soft tissue lesion attached to the pleura of the right upper lobe with estimated SUVmax = 18.4 denoting extra-nodal pleural disease.

Table 2 Comparison between PET-CT and CT results in Group I after the end of treatment.

Disease response in PET-CT		Disease response in CECT		
		Complete regression	Partial regression	Stationary
Complete regression	29	12	9	8
	96.7%	40%	30%	27%
Disease relapse	1	0	0	1
	3%	0%	0%	3%
Total	30	12	9	9
	100%	40%	30%	30%

Table 3 Comparison between PET-CT and CT results in Group I after the end of treatment.

Disease response in PET-CT		Disease response in CECT		
		Complete regression	Partial regression	Stationary
Complete regression	14	6	4	4
	70%	30%	20%	20%
Partial regression	2	0	2	0
	10%	0%	10%	0%
Stationary	4	0	1	3
	20%	0%	5%	15%
Total	20	6	7	7
	100%	30%	35%	35%

6.4. Extramediastinal LNs

Eleven cases had associated enlarged hilar lymph nodes. PET/CT showed complete regression in 8 cases (72.7%) of which CT agreed in 5 cases and showed partial regression in the other three. One case showed partial regression on PET/CT which was diagnosed as stationary course according to the CT findings. The last case showed stationary course in both methods.

We had 6 cases associated with axillary lymph nodes. PET/CT showed complete regression in 4 cases, partial regression in one case and progressive course in the last case. CT showed complete regression in 2 cases, partial regression in 4 cases, thus agreeing with PET/CT in 3 cases (50%).

6.5. Extra-nodal sites

We detected 10 cases with extra-nodal sites of thoracic lymphoma disease in our study; 5 cases had pathologically proven alveolar pulmonary infiltration (nodules or area of consolidation) (Fig. 4) pleural lymphomatous lesions ($n = 2$) and chest wall lesions ($n = 2$), bony lesion in the sternum ($n = 1$).

The estimated SUVmax in extranodal lymphoma was 8.8, 3.7 and 4.4 at initial study, after the first course of chemotherapy and at the end of treatment respectively. Thus PET/CT detected 6 cases with complete remission, 2 had stationary course, one with partial regression and only one case showed progression of the disease in the 2–4 months' follow up.

Four other cases (8%) showed tiny parenchymal nodules detected by CT (less than 5 mm) with no activity on PET/CT. We did not consider these nodules in the initial staging as we thought that they were probably non-specific inflammatory nodules. Nevertheless, lymphoma could not be totally excluded as their metabolic activity may be too low to be detected by PET/CT due to their tiny size. So, they were closely followed up and showed stationary size with absent metabolic activity confirming their benign nature.

We found a 100% sensitivity and specificity for PET-CT; compared to 62.5% sensitivity and 97.6% specificity for CECT in detection of extra-nodal disease sites.

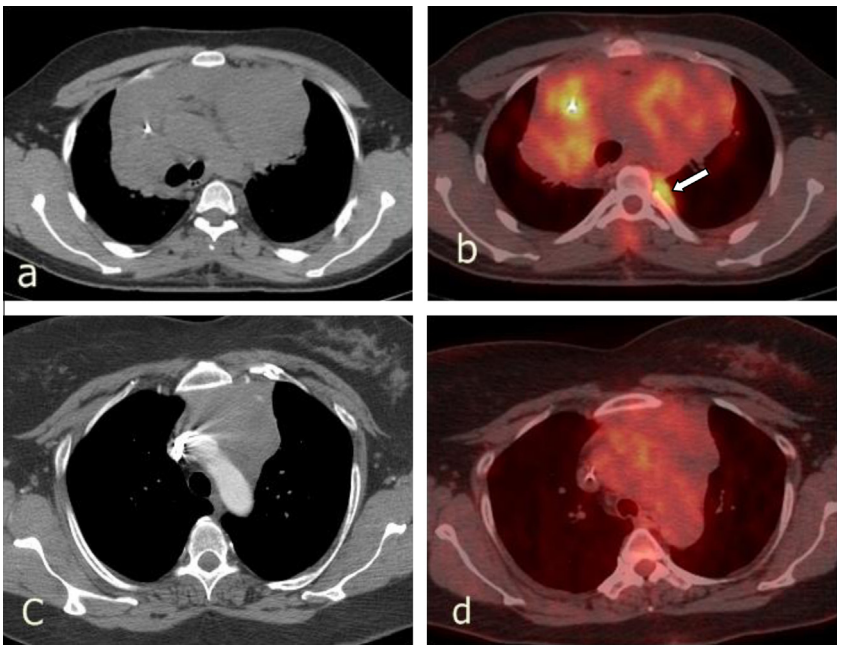

Fig. 4 Axial CECT (a) showing a large bulky mediastinal mass in a 33 year old male with Hodgkin lymphoma. PET-CT (b) shows an estimated SUVmax of 11.2. A right upper lobe patchy area of consolidation was also noted with SUVmax of 3 (arrow); 4 weeks after chemotherapy the CT shows regression in the size of the anterior mediastinal mass lesion (c) with no evidence of hyper metabolism in PET-CT denoting complete metabolic response in spite of partial regression in size. The consolidated lesion also showed complete response (d).

PET/CT was statistically significant ($P < 0.001$) in the follow up of mediastinal hilar lymph nodes. It also shows statistical significance in the follow up of axillary lymph nodes ($P = 0.046$).

7. Discussion

CT is the most readily available and most commonly used tool for staging lymphoma. Fundamental limitations of CT are that recognition of lymph node involvement is based solely on size and that detection of bone marrow and extra-nodal tissue involvement may be limited. In addition to depicting nodal sites of lymphoma with greater accuracy than CT, PET/CT can detect the activity of the lesion and has greater sensitivity for sites of extra-nodal involvement and correspondingly has been found to improve baseline staging compared with conventional staging with CT alone (13). Hodgkin's lymphoma is FDG avid, and PET/CT is more accurate in initial staging than CECT.

In this study PET/CT upstaged 5 cases (10%). PET/CT and CT were concordant in staging of the other 45 cases (90%). The concordant in staging in our study between PET/CT and CT was higher than that detected by Riad et al. They found a 73.2% concordance (14). Although it was agreeable with Pelosi et al. who found a 12% upstaging by PET/CT compared to CT (15) the additional value of PET/CT causing upstaging in our cases was not in detecting active subcentimetric lymph nodes as in the study conducted by Ranani et al. (16) but in detecting the extra-nodal thoracic sites of disease that were not determined by CECT. Downstaging of cases was documented in previous studies (15,16), as they detected enlarged lymph nodes by CT yet, not metabically active on PET/CT. No similar cases that needed downstaging were found in our study because our patients had early stage lymphoma disease.

An important and valid application of PET/CT is to detect viable tumor in residual lesions after the treatment of patients with HL and NHL. A residual mass at the end of therapy is not a rare finding and is considered a clinical challenge in HL and intermediate/high grade NHL restaging. FDG-PET has proved to be much more accurate in distinguishing fibrosis from viable tumor, since fibrosis does not show high metabolic activity in contrast to viable residual tumor (Figs. 1 and 4) (17). This fact made FDG PET/CT extremely useful for therapy response assessment.

Our study confirmed the value of PET/CT in initial staging and planning that involved field radiotherapy. We showed that PET/CT detected a 60% complete regression ratio compared to only 14% by CT scan. In the future this may be relied upon to minimize chemotherapy cycles in favorable group of patients, hence reducing the side effects of treatment (5).

A bulky mediastinal mass is often seen in patients with Hodgkin's lymphoma. Treatment of Hodgkin's lymphoma often results in size reduction of the mass, but complete disappearance of the mass is unusual. Detection of viable tumor in these residual masses is difficult with conventional imaging modalities (1). We had seven cases with bulky mediastinal masses (> 10 cm). All of them showed a significant decrease in size by CT scan, while PET/CT showed complete regression of the disease with no evident activity denoting fibrosis in four cases (Figs. 1 and 4). In one case it showed partial progression and in the last two cases PET/CT detected progressive course of the disease despite the considerable reduction in size of the mass lesion.

We found a 100% sensitivity and 96.7% specificity of PET/CT after the first line of treatment of mediastinal lymphoma which was comparable to previous studies (8,18).

In the second follow up study after the end of chemotherapy cycles, PET/CT and CECT were concurrent in results in 22 cases (44%) and discordant in 28 cases (56%) in contradiction to Zinzani et al. who showed much higher agreement percentage between both modalities (90%) and less disagreement (19).

In the study conducted by Ranani et al. few cases with pulmonary lesions interpreted as benign by the CT scan were read as lymphomatous infiltration on PET/CT (16). In our study, we reported 5 cases (10%) presenting with pulmonary disease at the time of initial diagnosis, all showed parenchymal lung nodules ranging between 2 and 4 cm in diameter on CT with patchy areas of consolidation. PET/CT showed positive activity with SUVmax ranging from 4.3 to 11.6 (mean SUVmax = 8), which was confirmed by CT guided biopsy as active lymphocytic alveolar infiltration. The other four cases with tiny parenchymal nodules detected by CT, that did not show activity on PET/CT were confirmed as benign by further follow up.

Axillary lymph node enlargement is usually nonspecific, however if associated with other pathological localizations it shows true positive results in most cases and is an indicator of high likelihood of disease recurrence (20). We had only four cases with associated axillary lymph node that showed a significant P value on PET/CT follow up.

Several studies compared CECT to PET/CT in detection of extra-nodal lymphoma; all were around 88% sensitivity and 100% specificity for PET-CT compared to 50% sensitivity and 90% specificity with CECT (6,18,21). We reported 100% sensitivity and specificity for PET-CT; compared to 62.5% sensitivity and 97.6% specificity for CECT in detection of extra-nodal disease sites.

Our study was limited by the absence of further follow up of the patients after 6 mo-2 years to detect the overall survival and time to progression to disease.

PET/CT proved higher sensitivity and specificity over CECT in our study. The major strength of PET/CT over CECT was its higher ability for detection of extra-nodal sites of lymphoma at initial staging and its much higher ability to exclude active disease in residual nodal mass lesions on follow up studies. The use of early response to therapy of lymphoma patients by PET/CT may tailor the dose of chemotherapy avoiding unnecessarily toxic treatment.

Conflict of Interest

The authors have no conflict of interest to declare.

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