

BEYOND PET/CT IN LYMPHOMA: DOES PET/CT HAS SIMILAR DIAGNOSTIC ACCURACY IN RECURRENT LYMPHOMA CASES IN TB-ENDEMIC COUNTRIES

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ABSTRACT

BACKGROUND: Lymphoma includes histologically heterogeneous group of tumors which are derived from the cells of the immune system. **OBJECTIVE:** The objective of this study is to determine the diagnostic accuracy of PET/CT in recurrence of lymphoma in treated cases. The PET CT findings were correlated with biopsy and histopathological diagnosis. **METHODS:** After ethical committee approval, this study was conducted in the PET/CT suite, Department of Radiology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan. The study design was cross sectional and sampling technique was non-probability and purposive. The sample size was 155 (Sample size estimated using 95% confidence level and 8% margin of error with an expected sensitivity value of PET/CT as 85% and specificity value as 95%). Patients of all age and both genders who had PET/CT avid disease on follow up scan after achieving complete response after first line of treatment. The patients who had a positive PET/CT were later discussed in MDT and were referred for biopsy. The biopsy of the patient was then performed in appropriate modality to document the exact histopathology which was gold standard in our study. **RESULTS:** Histopathology confirmed that a total of 70 patients recurrent disease of lymphoma patients. PET/CT correctly identified 64/70 of the recurrent cases of lymphoma. Thus the sensitivity of the PET/CT was 91.4%. On the other hand, PET/CT truly identified 37/85 cases without recurrent disease of lymphoma making the specificity as 43.5%. The Overall diagnostic accuracy of the PET/CT was 65.5%. Positive and negative predicative values for a diagnosis of recurrent disease of lymphoma on PET/CT were 57.7% and 86.0% respectively. **CONCLUSION:** We have found 65% diagnostic accuracy of PET/CT for detecting recurrent disease in the lymphoma patients which is lower than internationally published data i.e. 85%. Possible cause of this would be high burden of infectious diseases (particularly tuberculosis) in our society.

Key words: PET/CT; recurrent lymphoma; tuberculosis

Introduction

Lymphoma includes histologically heterogeneous group of cancers which are derived from the cells of the immune system.¹ The overall incidence of lymphoma in Asian population is 17.8 per 100,000 men

and 12 per 100,000 women.² The hallmark of the lymphomatous disease is the enlargement and proliferation of lymph nodes or secondary lymphoid tissues. Lymphoma is generally divided into two groups: Hodgkin's disease (HD) and an inhomogeneous group of conditions called non-Hodgkin's

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lymphoma (NHL).³ Both of these entities may arise from or involve almost any organ of the human body. The incidence of Hodgkin lymphoma in Pakistan is 1.1% and Non-Hodgkin lymphoma is 3.3% among other malignancies² and its trend is increasing when compared with other malignancies.⁴ According to Karachi (South) Cancer Registry (1995-1999) NHL is the 9th most common malignancy among males in Karachi and ranked 10th among the females.⁵ In a study conducted in Pakistan the male to female ratio was found to be 1.9:1.⁶

In the past, contrast-enhanced CT was the modality of choice for the imaging of the lymphoma patients.⁷ However, FDG PET has been now widely used for staging of disease, monitoring of treatment response and documenting residual and recurrent disease in lymphoma patients.⁸ It's because of the fact that contrast-enhanced CT has limited sensitivity in detecting disease in the normal-sized lymph nodes and other sites i.e. bone marrow, spleen and extra nodal tissue.⁷ The newer PET/CT system has got the advantage as addition of CT helps in anatomic correlation and thus has improved its sensitivity and specificity.¹ FDG PET/CT is extremely useful for therapy response assessment as it has the ability to distinguish between residual metabolically active tumor and areas of necrosis and fibrosis without any metabolic activity.⁷ The basic advantage of FDG PET/CT in documenting residual disease in both NHL and Hodgkin disease is mostly attributed to the detection of FDG-avid normal-sized lymph nodes (usually <1 cm) and of extra nodal sites that were previously missed or appear morphologically normal on CT i.e. liver, spleen, cortical bone, bone marrow and skin. However, in a few cases benign findings on CT in para spinal and pulmonary regions may be misinterpreted as malignant when they were seen with FDG PET/CT.⁷

FDG PET is a functional imaging modality³ and is based on the uptake of the radionuclide 'FDG' which is an analogue of glucose and its uptake is directly proportional to the glucose metabolism of tissue and is higher in tumor cells. The FDG uptake is measured as standard uptake value (SUV) which is the semi quantification of activity within an area of interest based on administered FDG activity and patient body weight. FDG PET/CT can help confirm the absence of active lymphoma cells after treatment but because

of some false positives, histological confirmation or further follow-up may be required.⁹ A value of more than 3 should raise the possibility of malignancy though the possibility of false positive results remains as lesions with inflammation only can have higher SUV value.⁹ This may be a particular problem in Pakistan because of high incidence of infectious and granulomatous diseases. The documented positive predictive value of PET/CT is 85%⁹ with sensitivity and specificity of 96% and 100% respectively in the restaging of lymphoma patients.¹⁰

The purpose of our study is to calculate local data from PET/CT regarding the sensitivity, specificity and positive predictive value in a population where there is risk of false positive cases due to high incidence of granulomatous disease specifically tuberculosis and compare it with international data which basically obtained from low incidence population. Another purpose is to set local guidelines in cases of recurrent lymphoma whether only PET/CT finding would be enough to start the treatment or not.

Materials and Methods

After ethical committee approval, this study was conducted in the PET/CT suite, Department of Radiology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan. The study design was cross sectional and sampling technique was non-probability and purposive. The sample size was 155 (Sample size estimated using 95% confidence level and 8% margin of error with an expected sensitivity value of PET/CT as 85% and specificity value as 95%). Patients of all age and both genders who had PET/CT avid disease on follow up scan after achieving complete response after first line of treatment including chemotherapy and/or radiotherapy were included in this study. Newly diagnosed patients who had not received any therapy, pregnant patients and patients without consent were excluded from study.

PET/CT imaging protocols:

Those patients referred from the medical and pediatric oncology department for follow-up scan after achieving complete response after their planned first line of treatment were evaluated. Patients were asked to

take nothing per oral for atleast 4-hours prior to the scan and were also directed to avoid high protein diet 24 hours before the scan. On the day of the exam after obtaining demographic data, history, physical examination, written informed consent and blood sugar level test, the patients were asked to rest for at least 15 minutes prior to the injection of radio-pharmaceutical, so as to decrease the effect of the muscular activity which can increase the rate of false positive findings. A calculated dose of recently produced 18F-FDG was injected as a bolus intravenous injection preferably in upper limb. Patient was then kept in isolation to protect others personals from radiation for at least 45 minutes. A spiral CT scan for attenuation correction is obtained first, after which PET data are acquired. The patient was asked to keep the same position during scan so that the effect of misregistration could be decreased. Typical whole-body CT parameters include: 120kV, 240 mAs, 1.5 mm collimation, 40 cm FOV, soft tissue and bone window settings. Mean time for FDG uptake period is 60 minutes per patient. The dose for adult patient is 350-450 MBq depending on patient's weight and 5 MBq/Kg of body weight. Philips Gemini TF16 DS PET/CT scanner was utilized for imaging with FOV of 55-60 cm for PET and 45-50 cm for CT with resolution of 4-6 mm. PET data acquisition is usually started after CT with 3-6 min per bed position for a total of seven to nine beds covering the area from the mid-forehead to the proximal thigh. Typical whole-body PET parameters include: 168 PET matrix, 4 iterations, 8 subsets, 4-mm pixel size. For the head and neck area, PET acquisition parameters can be changed as follows: 6-12 min bed time, 256 PET matrix, 6 iterations, 4 subsets, 1.82-mm pixel size. As based on the experience in our institution, it is of utmost importance to obtain HR PET/CT images through the head and neck region with a separate acquisition from the body part to allow for detection of small lesions. Iterative reconstruction was later done on PET-CT scanner. In few cases delayed phases were also obtained depending on the fact that any abnormal uptake was seen in bowel or further imaging of the whole limbs if abnormal uptake was seen in the initially scanned skeleton. SUV were calculated with the help of PACS software for all the PET avid regions detected in the acquired data which helped in quantification of uptake of tracer in the suspected lesion and CT

imaging provided the size and anatomical location of the lesion. Image interpretation was done separately by a Radiologist and a Nuclear Physician. The patients who had a positive PET/CT were later discussed in MDT and were referred for biopsy. The biopsy of the patient was then performed in appropriate modality to document the exact histopathology which was gold standard in our study. All this information was recorded in a predesigned Performa by the researcher.

STATISTICAL ANALYSIS:

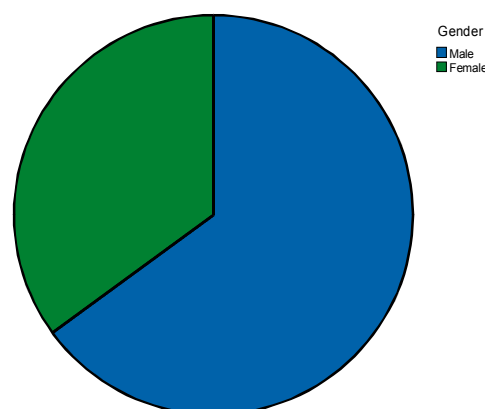
The data analysis was carried out using computer based Statistical Package for Social Sciences (SPSS) 16 version. Quantitative variables such as age were presented in the form of mean \pm S.D. Frequencies with percentages were calculated for categorical variables like sex, final diagnosis on biopsy and PET/CT. The binary variables of diagnosis of recurrent disease in lymphoma patients on histopathology and PET/CT were cross tabulated to construct a 2x2 table. The two by two table was used to calculate sensitivity, specificity, positive predictive value (NPV), negative predictive value (PPV) and diagnostic accuracy (DA) according to the formulae described above.

Results

Out of 155, the study included 101 (65%) male patients and 54 (35%) female patients (Tab. 1 and Graph 1).

Gender	Count
Male	101
Female	54

Table 1: shows gender distribution among patients included in this study. (n=155)



Graph 1: Pie chart showing gender distribution among patients included in this study. (n=155)

The mean age of patients was 39.01 years with standard deviation of ± 17.40 . The minimum and maximum age of the patients was 12 years and 69 years respectively (Tab. 2).

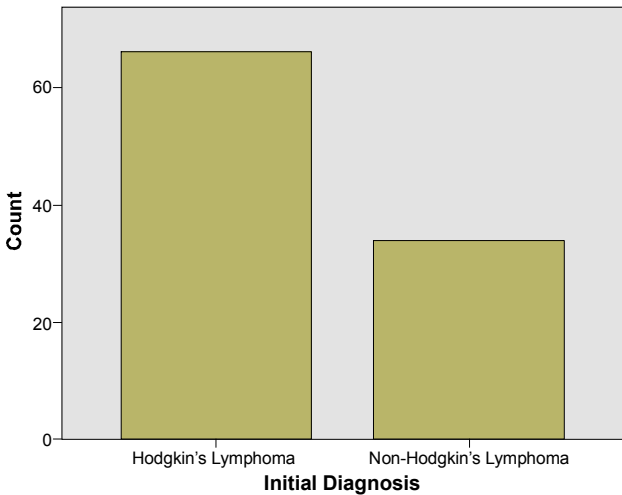
	N	Minimum	Maximum	Mean	Std. Deviation
Age	155	12	69	39.01	17.407
Valid N (listwise)	155				

Table 2: shows age distribution among patients included in this study. (n=155)

Out of the total patients 102 (66%) patients initially had the diagnosis of Hodgkin's Lymphoma while the rest 53 (34%) were diagnosed patients of NHL. There were all biopsy proven patients and had completed their first line chemotherapy and were on follow up (Tab. 3 and Graph 2).

Initial Diagnosis	Count
Hodgkin's Lymphoma	102
Non-Hodgkin's Lymphoma	53

Table 3: demonstrates distribution of patients according to initial diagnosis.



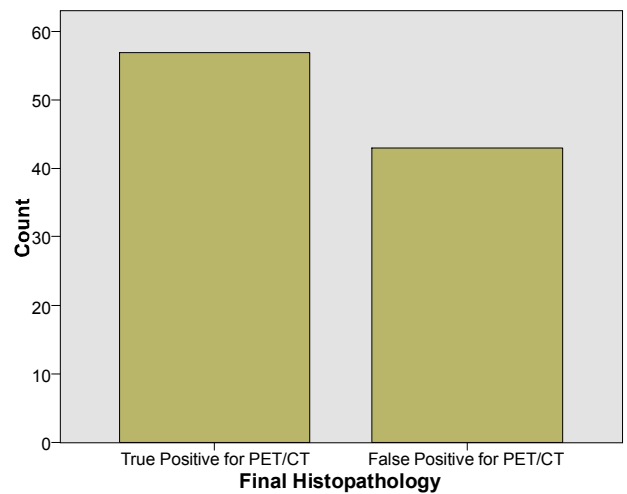
Graph 2: shows bar chart showing distribution of patients according to initial diagnosis.

All the patients had their PET/CT on follow or on the clinical suspicion of recurrent disease. The maximum calculated SUV of the lesion in lymphoma patients was found to be 14.3 with mean of 8.51. The maximum SUV was calculated to be 14.3 with minimum SUV of the positive lesion to be 3.2. (Tab. 4) These patients were labeled as PET/CT positive patients. Most of them were discussed in MDT for a possible biopsy. All these patients underwent biopsy by the possible

	N	Minimum	Maximum	Mean	Std. Deviation
SUV of Lesion	155	3.2	14.3	8.512	3.3157
Valid N (listwise)	155				

Table 4: Shows minimum, maximum and mean SUV of the lesions in PET/CT.

image guidance and histopathology was seen. The 57% of the patients who underwent biopsy were proven malignant and were labeled as true positive for PET/CT while the rest 43% patients had negative biopsy for malignancy (Graph 3). (Tab. 7) shows the list of diagnosis which resulted in false positive result for PET/CT in 48 cases.



Graph 3: Depicts bar chart showing distribution of patients into true positive and false positive group for PET/CT on the basis of final histopathology report.

	Histopathology +ve	Histopathology -ve	
PET/CT + ve	64	48	Total PET/CT +ve 112
PET/CT - ve	06	37	Total PET/CT -ve 43
	Total Histopathology +ve 70	Total Histopathology -ve 85	Total Patient 155

INTERPRETATION:

True Positive, n = 70 False Positive, n = 48
 True Negative, n = 37 False Negative, n = 06

Table 5: shows cross tabulation for the results of histopathology & PET/CT

Histopathology confirmed that a total of 70 patients recurrent disease of lymphoma patients. PET/CT correctly identified 64/70 of the recurrent cases of

Statistical Measure	Percentage	Number
Sensitivity	91.4%	64/70
Specificity	43.5%	37/85
Accuracy	65.5%	101/155
Positive predictive value (PPV)	57%	64/112
Negative predictive value (NPV)	86.0%	37/43

PPV = Positive Predictive Values NPV = Negative Predictive Values

Table 6: shows statistical results for PET/CT taking histopathological results as gold standard.

Number of false positive cases	Histopathological diagnosis	Percentage
40/48	Mycobacterium tuberculosis	83.33%
5/48	Non-specific inflammation	10.41%
2/48	Fungal lymphadenitis	4.16%
1/48	Sarcoidosis	2.08%

Table 7: reveals alternate diagnosis that resulted in false positive PET CT results.

lymphoma. Thus the sensitivity of the PET/CT was 91.4%.

On the other hand, PET/CT truly identified 37/85 cases without recurrent disease of lymphoma making the specificity as 43.5%.

The Overall diagnostic accuracy of the PET/CT was 65.5%. Positive and negative predicative values for a diagnosis of recurrent disease of lymphoma on PET/CT were 57.7% and 86.0% respectively.

Discussion

Lymphoma is one of the most common malignant diseases which is actually a lymphoproliferative disorder and is divided into two major groups including Hodgkin's and non-Hodgkin's lymphoma.¹¹ It basically arises from the white blood cells called lymphocytes. Recurrent disease is the emerging issue in this disease after the patient is being treated with first line therapy¹² and it is known that 20 to 50% of the patients have recurrent disease. Lymphoma being a very chemo / radiation sensitive therefore early diagnosis of the recurrent disease is very important. F18-FDG PET is now becoming popular in the staging and follow-up of lymphoma patients and is replacing the previous nuclear medicine studies and radiological

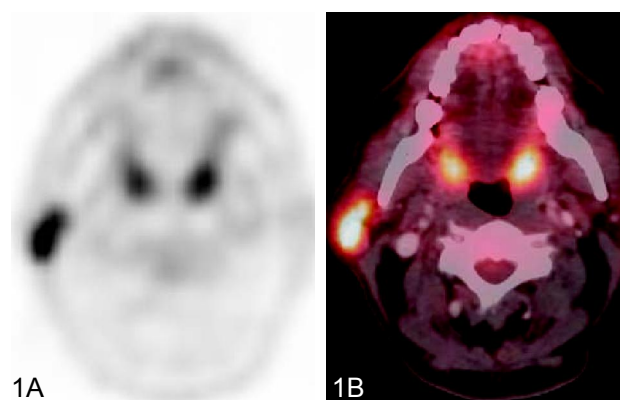
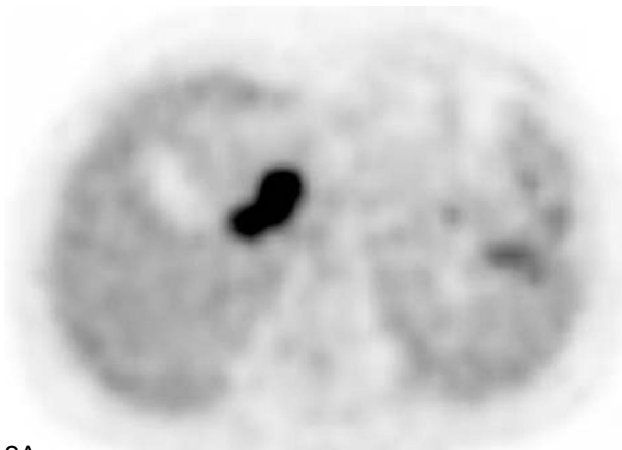


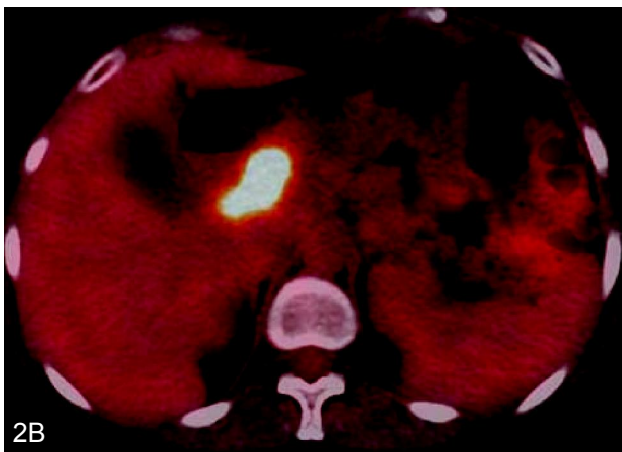
Image 1 (a and b): PET only image and combine PET CT image respectively. Young patient presented with right cervical lymphadenopathy having past history of treated mixed cellularity Hodgkins lymphoma. Suspicion of recurrent disease was made and PET CT was advised which showed right level II cervical lymph node with FDG avid uptake with SUV of 9. Excision biopsy was performed before the start of treatment which revealed granulomatous inflammation and tuberculosis.

studies including Gallium-67 scan and CT scan¹³ as it better helps in differentiating the recurrent disease from scar, fibrosis or active tumor.¹⁴

In this cross sectional survey, 155 patients were included who were selected according pre-decided inclusion and exclusion criteria. The mean age of patients was 39.01 years with standard deviation of ± 17.40 including 65% of the male patients and 35% female patients. All these patients were positive for recurrent disease and after discussion in multi disciplinary team (MDT) meeting were referred for image guided biopsy which included US / CT guided biopsies, Bronchoscopic guided biopsies, endoscopic ultrasound guided biopsies and bone marrow biopsy depending on the imaging findings. The positive predictive value calculated in this study was 57% as compared to the average internationally published value of 85%.⁹ Guay et al published one prospective study in 2003, which revealed the sensitivity and specificity of FDG PET to predict relapse are 79 % and 97 %, respectively, with a negative predictive value more than 90 % in HL patients after the completion of chemotherapy. Similar study also concluded that negative PET study is also an excellent predictor of good prognosis.¹⁵ A retrospective review of 27 patients found that all 15 patients with residual biopsy-proven disease and 11 of 12 patients who were disease free were correctly identified with ¹⁸F-FDG PET (48). ¹⁸F-FDG PET had a higher specificity



2A



2B

Image 2 (a and b): PET only image and combine PET CT image and respectively. A case of treated Non-hodgkin lymphoma (NHL) presented with abdominal pain and low grade fever. Imaging was performed to exclude recurrent disease has shown portohepatic nodal mass showing high FDG uptake with SUV of 11.3. According to departmental protocol image guided biopsy of the node was advised before starting the treatment. Biopsy revealed granulomatous infection and patient was treated with antituberculous therapy and recovered completely on followup.

(92% vs. 17%, $P < 0.01$), accuracy (96% vs. 63%, $P < 0.05$), and positive predictive value (94% vs. 60%, $P < 0.05$) than did CT.¹⁶ Another study on published in 2006 mentioned the use of FDG PET for therapy response assessment in Hodgkin disease and aggressive NHL in restaging. They reported pooled sensitivity and specificity for the detection of residual disease after completion of first-line therapy are 84% and 90%, respectively, for Hodgkin disease, and 72% and 100%, respectively, for aggressive NHL.¹⁷ Comparing our data with these international values shows there is significant statistical difference with lower values which should be considered during

treatment and staging of lymphoma. The reason is the possibility of high incidence of granulomatous disease in Pakistan.

In our study most of the patients who had a negative biopsy for malignancy were proven to have granulomatous infection particularly tuberculosis and were treated for it accordingly. This is because of the known fact that Pakistan rank amongst top 10 countries having high rate of tuberculosis as is reported to be at 6th place.¹⁸ So bearing in mind this high load of granulomatous disease in Pakistan this will obviously affect the effectiveness of PET/CT in diagnosing the malignant disease and in particular the lymphoma. This is a single center study performed in one of the city of Pakistan and hence to validate this study and to revise local protocol there should be more similar studies performed on multi-center data in the future. This study is considered first of its type and should be considered pioneer study while doing similar type of studies in the future.

Conclusion

We have found 65% diagnostic accuracy of PET/CT for detecting recurrent disease in the Lymphoma patients which is lower than internationally published data i.e. 85%. Possible cause of this would be high burden of infectious diseases (particularly tuberculosis) in our society. Our recommendations according to this study are "Positive results in PET/CT should not be enough to label the patient with recurrent disease and should always accompany with biopsy for accurate diagnosis and prompt treatment in our setup"

Conflict of Interests:

The authors declare that there is no conflict of interests in relation to this work.

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