Section: Miscellaneous

Original Research Article

TO DETERMINE BONE MARROW INVOLVEMENT USING 18F-FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY SCAN AND ITS CORRELATION WITH BONE MARROW BIOPSY IN STAGING AND DIAGNOSIS OF LYMPHOMA: A PROSPECTIVE STUDY AND CLINICAL EXPERIENCE FROM THREE TERTIARY CARE CANCER INSTITUTES OF INDIA

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Abstract

Background: ^{18}F-fluorodeoxyglucose positron-emission computed-tomography (18FDG- PET-CT) scan is extensively used in the diagnosis and staging work-up of lymphomas. Bone marrow biopsy (BMB) is done to know if lymphoma has spread to bone marrow as part of staging. The aim of this study was to detect the bone marrow involvement using PET-CT and correlation with BMB in diagnosis and staging of lymphoma. **Materials and Methods:** A prospective study was conducted in the departments of nuclear medicine and oncology in three tertiary care cancer institutes of India over a period of two years from March 2019 to March 2021 on 105 patients which included 35 cases of Hodgkin's lymphoma and 70 cases of non-Hodgkin's lymphoma. **Result:** In Hodgkin's lymphoma cases, BMB and PET-CT findings were concordant in 71% of the cases. The sensitivity of PET-CT was 100% when compared to BMB in cases of Hodgkin's lymphoma. For aggressive NHL cases revealed that sensitivity of PET-CT was 70% in detecting bone marrow involvement while indolent NHL cases, analysis of the data revealed a sensitivity of 37.5%. **Conclusion:** PET-CT improved our ability to correctly stage the disease in patients of lymphoma by detecting the bone marrow involvement; especially in cases of Hodgkin's lymphoma and aggressive non-Hodgkin's lymphoma, changing the stage of the patient directly to Stage IV, thus altering the management in certain cases. PET-CT detected bone marrow involvement in cases that were missed by/ inaccessible for BMB, thus changing the stage of disease and further helping in planning and management of the disease.

INTRODUCTION

Among all cancers, lymphoma including non-Hodgkin's lymphoma (NHL) and Hodgkin lymphoma (HL) is eighth most frequently diagnosed cancer.[1,2] In children, they are the third-most common cancer.[2] In India too, the incidence of lymphomas has shown an increase in the last decade in Indian population too.[3-5] Lymphoma is a group of blood cell tumors that develop from the lymphatic system. The cancer affects immune cells called lymphocytes, which are white blood cells which divide faster than normal or live longer than they are supposed to causing abnormal increase in the number of these cells. NHL can broadly be classified into two prognostic groups: The aggressive and the indolent lymphomas, the latter group having a better prognosis, with a median survival spanning about 10 years. Of the aggressive lymphomas, diffuse large B-cell lymphoma (DLBCL) is the most common, accounting for about 30% of cases, followed by mantle cell lymphoma (MCL) and adult T-cell leukemia/lymphoma, which represent 6 and 8% of NHL cases, respectively. The most common type of indolent lymphoma is the follicular lymphoma (FL) which represents 22% of NHL cases, followed by

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marginal zone lymphoma (MZL) and small-cell lymphocytic lymphoma (SLL) representing 6% and 8% of cases, respectively. HL is a potentially curable lymphoma, more common in males, except for the nodular sclerosis variant, which is slightly more common in females.[6] Most common sites include lymph nodes, spleen, bone marrow, blood or other organs. Lymphoma typically originates in the lymph nodes. Sites of extra-nodal lymphoma includes tonsils, skin, brain, bowels and bone. Lymphoma most often spreads to the lungs, liver, and/or brain. Bone marrow biopsy (BMB) is an important part of the routine staging of lymphoma as marrow infiltration is of prime importance not only in staging the disease but also in the tailoring of treatment protocols.[7,8] Fluorine-18 (18F)- fluorodeoxyglucose (FDG) has found widespread use in the diagnosis and staging work-up of lymphomas. One of the most promising applications is in the determination of clinical stage of disease at presentation or recurrence,[9-11] Accurate staging is essential for planning an effective treatment regimen and minimizing side effects and toxicity.[12] Treatment may involve one or more of the following: chemotherapy (CMT), radiation-therapy (RT) , targeted therapy (TT), and surgery.

MATERIALS AND METHODS

Study site, facilities and population

A prospective study was conducted in the department of nuclear medicine in collaboration with department of oncology over a period of two years from March 2019 to March 2021 in three tertiary care cancer institutes of India. The patients belonged to any sex, race or ethnicity from both rural and urban background The study was duly approved by institutional ethical and scientific committee and in accordance to1964 declaration of Helsinki. The following facilities were used to carry out our project; 1. PET-CT scanner- Siemens Biograph; 2. Medical Cyclotron- Siemens Eclipse- 11MeV dual beam multi-target medical cyclotron; 3. Requisite facilities for taking bone marrow biopsy sample of the patient. Random sampling method was used to select the patients. This study was performed on 105 patients of histologically/cytologically proven lymphoma. Formula for sample size calculation was:

$$n = \frac{X^2 * N * P * (1-P)}{(ME^2 * (N-1)) + (X^2 * P * (1-P))}$$

Where :

n = sample size

X^2 = Chi – square for the specified confidence level at 1 degree of freedom

N = Population Size

P = population proportion

ME = desired Margin of Error (expressed as a proportion)

Inclusion and exclusion criteria

Patients included were diagnosed cases of HL and NHLs who had given informed consent. Age criteria included <10 years to 80 years with Karnofsky Performance Status (KPS) of 60- 70%. Those excluded were patients unwilling to give consent for the study, unable to lie supine for imaging with PET-CT, claustrophobic patients, KPS <60%, pregnant ladies and blood sugar (random) >150 mg%.

Procedure followed during staging by PET-CT

Over a period of two years, 105 consecutive patients underwent FDG-PET-CT examination. The inclusion criterion for the study was the diagnosed case patients of lymphoma. The PET findings of the primary tumor at forty minutes were analysed for bone marrow involvement and compared with bone marrow biopsy findings. Tumor FDG uptake was quantitated with the maximal pixel standardized uptake value (SUV). The study was carried out in the following steps: -

Step 1: Detailed history of the lymphoma patients referred from the Oncology dept for whole body PET-CT scan will be recorded. Findings of relevant investigations carried out including bone marrow biopsy findings will be recorded.

Step 2: PET-CT scan will be performed after forty minutes of injecting F-18 FDG using Siemens Biograph-2 scanner.

Step 3: The outcome of the results will be tabulated and analyzed to assess the correlations between 18F-FDG uptake in the bone marrow at forty minutes and the findings of bone barrow biopsy.

The results of bone marrow biopsy were taken positive when it revealed presence of lymphoma cells in the bone marrow specimen. 18F-FDG PET-CT was considered positive for bone marrow involvement in cases of uni- or multifocal bone marrow 18F -FDG uptake that could not be explained by benign findings on the underlying CT image or history. A final diagnosis of bone marrow involvement was considered if the bone marrow biopsy was positive or if the positive 18F -FDG PET-CT was confirmed by guided biopsy or in cases of disappearance of focal bone marrow uptake concomitant with the disappearance of uptake in other lymphoma lesions on 18F -FDG PET-CT monitoring.

PET- CT scanner

PET study was done using a whole-body full-ring dedicated LSO detector PET-CT scanner (Biograph 2). CT images were obtained using 130KV and 25mAs (mean) without administration of oral or intravenous contrast. CT based attenuation correction were done. Images were reconstructed using standard iterative algorithm (OSEM) and reformatted into short axis, vertical and horizontal long axes views. A 3D image and fusion images of PET and CT were obtained.

Statistical Analysis

The results of bone marrow biopsy were taken positive when it revealed presence of lymphoma cells in the bone marrow specimen. 18F-FDG PET-CT was considered positive for bone marrow involvement in cases of uni- or multifocal bone marrow 18F -FDG uptake that could not be explained by benign findings on the underlying CT image or history. A final diagnosis of bone marrow involvement was considered if the bone marrow biopsy was positive or if the positive 18F -FDG PET-CT was confirmed by guided biopsy or in cases of

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disappearance of focal bone marrow uptake concomitant with the disappearance of uptake in other lymphoma lesions on 18F -FDG PET-CT monitoring. Chi-square test was used for nominal data and sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) calculated with respect to BMB. Power greater than 80% significance level was considered as 0.5 in the analysis. All quantitative data were expressed as medians (ranges).

RESULTS

In our study a total of 105 cases were included, males were 60 (59%) and females 45 (41%). Of these, there were 35 cases of HL while 70 cases were of NHL. 31 cases were indolent (low grade) NHL and 39 cases were aggressive (high grade) lymphoma. The median age for females was 39 years (5-75 years) and the median age for males was 35 years (4-80 years). Age-wise distribution of all types of lymphoma cases have been shown in [Table 1] while the age-wise distribution of cases detected with BMB and PET-CT are as per [Table 2]. True-positives were patients with a positive BMB and PET-CT scan. True-negatives were patients with a negative BMB and PET-CT scan. False-positive cases were those with positive PET-CT and negative BMB. False-negative cases were those with negative PET-CT and positive BMB. Table 3 shows that in this study, 18F-FDG PET-CT and BMB findings were concordant in 77 cases (73%); being concordant positive in 14 and concordant negative in 63 patients. In 15 patients, the PET scan showed increased FDG uptake but staging bone marrow biopsy was negative. In 13 patients the bone marrow biopsy specimen was positive but the PET scan normal; 2 of these 13 patients had NHL-DLBCL, 1 was NHL-High grade large cell lymphoma (Anaplastic cell), 2 had Follicular lymphoma, 3 had Splenic marginal zone lymphoma; rest were other low-grade NHL whose malignant cells did not take up FDG at lymph node or marrow disease sites. Hence, "True-positive cases" were 14 whereas "True-negative cases" were 63. "False-positive cases" were 15 while "False-negative cases" were 13. Further analysis revealed that out of 35 cases of HL, 18F-FDG PET-CT and BMB findings were concordant in 25 cases (71%); of which 1 case was concordant positive. However, PET-CT scan was positive in 10 more cases (approximately. 28.5%) in which BMB did not reveal involvement by lymphoma cells. In aggressive NHL cases out of 39 cases, BMB was concordant with 18F-FDG PET-CT in 32 cases (82%); of which 7 cases concordant positive. However, findings were found to be discordant in 7 cases (18%; 4 cases having PET-CT positive but BMB negative while 3 cases having BMB positive but PET-CT negative). In indolent NHL cases of the 31 cases, concordant findings were found in 20 cases (64%); of which 6 were concordant positive. In 11 cases, discordant findings were noted (10 cases had BMB positive but PET-CT positive and 1 case of PET-CT positive but BMB negative).

The sensitivity of the study was found to be low (51.9%); mainly because in indolent (low grade) NHL, the bone marrow involvement was not detected due to low FDG avidity of these type of lymphomas.59,60 The specificity of the study was however, found to be 80.8%. Also, the PPV and NPV of the study were calculated to be 48.3% and 82.9% respectively. In HL cases, BMB and PET-CT findings were concordant in 71% of the cases. It was found that PET- CT was able to detect single case of BM involvement that was detected using Bone marrow biopsy. Also, PET-CT has detected 10 more cases that were missed/not detected by BMB **[Figure 1].** The sensitivity of PET-CT was 100% (not reliable due to very small sample size) when compared to BMB in cases of Hodgkin's lymphoma. Negative predictive value of the study was also found to be 100%. Accuracy was found to be only 71.4% because a greater number of cases of bone marrow involvement were detected by PET-CT as compared to BMB. Analysis of data for aggressive NHL cases revealed that sensitivity of PET-CT was 70% in detecting bone marrow involvement. Also, PET-CT detected 11 cases in which bone marrow involvement was detected. Bone marrow biopsy revealed 10 cases of bone marrow involvement. Of these, 7 cases were detected by both PET-CT and BMB [Figure 2]. Specificity of PET-CT in detecting BM involvement was found to be 86%. PPV and NPV were 63.6% 89.3% respectively. PET-CT was able to detect correctly BM involvement (accuracy) in 82% of the cases. In indolent NHL cases, analysis of the data revealed a sensitivity of 37.5% which was close to 40% reported by Khan et al,[13] for sensitivity of BMB. The specificity of PET- CT was 93.3%. PPV and NPV were found to be nearly 86% and 58% respectively. PET-CT was able to accurately detect BM status in 64% of the cases [Table 4].

Table 1: Age-wise distribution of cases according to histology.

S No.	Age group (years)	Types of lymphomas			Total n/N (%)
	(<10-80)	HL n/N (%)	High grade NHL n/N (%)	Low Grade NHL n/N (%)	
1.	<=10	05/10	02/10	03/10	10/105
		(50)	(20)	(30)	(9.52)
2.	11-20	07/13	03/13	03/13	13/105
		(53.8)	(23.1)	(23.1)	(12.38)
3.	21-30	12/15	02/15	01/15	15/105
		(80)	(13.3)	(6.7)	(14.29)
4.	31-40	06/15	05/15	04/15	15/105

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		(40)	(33.3)	(26.7)	(14.29)
5.	41-50	01/7	04/7	02/7	7/105
		(14.3)	(57.1)	(28.6)	(6.67)
6.	51-60	03/21	10/21	08/21	21/105
		(14.3)	(47.6)	(38.1)	(20)
7.	61-70	01/18	09/18	08/18	18/105
		(5.56)	(50)	(4.44)	(17.14)

Table 2: Age-wise distribution of cases detected with Bone Marrow Aspirate/Biopsy and PET-CT

S No.	Age group (years)	BMB		PET-CT	
	(<10-80)	Involved n/N (%)	Not Involved n/N (%)	Involved n/N (%)	Not Involved n/N (%)
1.	<=10	02/10 (20)	08/10 (80)	02/10 (20)	08/10 (80)
2.	11-20	02/14 (14.3)	12/14 (85.7)	08/14 (57.14)	06/14 (42.86)
3.	21-30	0/15 (0)	15/15 (100)	04/15 (26.67)	11/15 (73.33)
4.	31-40	04/15 (26.67)	11/15 (73.33)	02/15 (13.33)	13/15 (86.67)
5.	41-50	02/7 (28.57)	05/7 (71.43)	027 (28.57)	05/7 (71.43)
6.	51-60	06/20 (30)	14/20 (70)	05/20 (25)	15/20 (75)
7.	61-70	09/18 (50)	09/18 (50)	06/18 (33.33)	12/18 (66.67)
8.	71-80	02/6 (33.33)	04/6 (66.67)	0/6 (0)	06/6 (100)

Table 3: Concordance between PET and BMB in all types of lymphomas

S. No	Lymphoma (N)	Marrow Involvement	Bone Marrow Aspirate/Biopsy findings		Total n/N (%)
			Involved n/N (%)	Not involved n/N (%)	
1.	HL (35)				
	PET/CT findings	Involved n/N (%)	01	10	11
		Not involved n/N (%)	0	24	24
2.	Aggressive NHL (39)				
	PET/CT findings	Involved n/N (%)	07	04	11
		Not involved n/N (%)	03	25	28
3.	Indolent NHL (31)				
	PET/CT findings	Involved n/N (%)	06	01	07
		Not involved n/N (%)	10	14	24
4.	Overall (105)				
	PET/CT findings	Involved n/N (%)	14/29 (48.27)	15/29 (51.72)	29/105 (27.62)
		Not involved n/N (%)	13/76 (17.1)	63/76 (82.89)	76/105 (72.38)

Table 4: Sensitivity, specificity, PPV, NPV and Accuracy of PET/CT and BMB in evaluation of bone marrow infiltration

S No.	Type of Lymphoma	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
1.	HL	100	70.6	9.1	100	71.4
2.	Aggressive NHL	70	86.2	63.6	89.3	82.1
3.	Indolent NHL	37.5	93.3	85.7	58.3	64.5
4.	Overall	51.9	80.8	48.3	82.9	73.3

DISCUSSION

HL is less common as compared to NHL but more common in young adults.[14] It shows bimodal peak: the first in young adulthood (age 15–35) and the second in those over 55 years old although these peaks may vary slightly with nationality.[15] Median age at diagnosis was 39-42 years.[15,16] Incidence of HL is more common in males as compared to females with male to female ratio at approximately 1.3:1.[16] Incidence of HL in US in the year 2016 was 2.6 per 100,000 men and women per year.[16] The crude incidence rates in 2013 were 4 new HL cases for every 100,000 males in the UK and 3 for every 100,000 females.[16,17] Incidence in India was noted as 1/25000 with classical HL 88% and nodular lymphocyte predominance HL (NLPHL) 12% cases in a single study.[18] In our study, maximum number of cases was detected in the age group of 15-35 (19 out of 36 – 52%) in concordance with the international statistics. Also, male preponderance was noted (20 out of 36 cases) with male to female ratio of 1.25:1 – similar to international statistics.[19,20]

NHL is more common as compared to HL with 90% of the lymphomas are NHL, incidence increases with age,[3] with median age at diagnosis is 66 years.[3,22] Incidence of is more common in males as compared to females with male to female ratio at approximately 1.2-1.4:1.[17,23,24] Incidence of NHL in US in the year 2016 was 19.5 per 100,000 men and women per year.[22] The crude incidence rates in 2013 were 23 new NHL cases for every 100,000 males in the UK and 19 for every 100,000 females.[22] In India, its incidence is on the upsurge with the current Age Adjusted Incidence Rates for males ranging from 1.0 (Meghalaya) – 6.2 (Delhi) per 100,000 in urban registries and for females from 0.7 (Meghalaya) – 4.6 (Delhi). The age-adjusted incidence rates for NHL in are men 2.9/100,000 and women 1.5/100,000.[25] In our study, a greater number of cases detected were of NHL (70 out of 105). Male preponderance was noted (40 out of 70). Male to female ratio was 1.33:1 (comparable to international statistics). Median age and mean age were found to be 56.5 years and 48.9

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years respectively for all types of NHL. For aggressive NHL, median age and mean age were found to be 55 years and 49.9 years respectively. For indolent NHL, median age and mean ages were 58 years and 47.7years respectively.

In a study by McKenna RW,[26] lymphoma in the BMB was found in 50% to 80% of patients with low-grade NHL, 25% to 40% of high-grade NHL, and 5% to 14% of HD patients at diagnosis. In yet another study by Conlan MG et al,[21] bone marrow lymphoma was present in 39% of low-grade, 36% of intermediate-grade, and 18% of high-grade lymphomas. Lots of studies have reported BMB to be unreliable method to detect bone marrow involvement because it results in only a small sample which may turn out to be inconclusive. Even if the volume of the biopsy is adequate, focal lesions can be missed. Sensitivity and specificity of BMB as reported by Khan et al,[13] were 40% and 100% respectively. These studies show that sensitivity of BMB to detect BM involvement is low and it is very unreliable.[27,28] In our study, overall sensitivity and specificity of PET-CT as compared to BMB was found to be 51.9% and 80.8%. In cases of HL, sensitivity and specificity were 100% (not reliable due to very small sample size) and 72.7% respectively. PET-CT detected 10 additional cases of BM involvement as compared to BMB in patients with Hodgkin's lymphoma. In patients with aggressive NHL, sensitivity was 70% which is much higher than the sensitivity reported with other studies.[13] In patients with indolent NHL, sensitivity was 37.5% which, though low, is nearly comparable with other studies.[29] However, the NPV and accuracy were found to be low (58.3% and 64.5% respectively) in indolent NHL cases. High false negative result noted in the indolent NHL is due to low FDG avidity of this type of lymphoma. False positive results (uptake noted in PET-CT but not on BMB) can be due to: -

1. The site may be inaccessible to biopsy.
2. In cases of heterogeneous uptake, bone marrow biopsy may not have been taken from the site actually involved.
3. Trauma – due to accident or the site of bone marrow biopsy.
4. Reactivation of bone marrow in cases of anaemia.

On follow up PET-CT, it was found that the abnormal bone marrow uptake disappeared in 13 cases which is a strong indirect evidence of bone marrow involvement by lymphoma cells. In one case, FDG avidity of the original disease of right tibia decreased in intensity. PPV was found to be low due to large number of false positive cases in HL. From this study we can note that sensitivity of PET-CT is either comparable (in Indolent NHL) or higher than BMB (in Aggressive NHL and HL).

Limitations of the study

The major limitation that was noted in this study was in diagnosis of bone marrow involvement in cases of indolent NHL. These lymphomas have been documented to have poor FDG uptake. Due to this poor uptake of FDG, PET-CT was not able to pick up bone marrow involvement in many patients of these types of lymphomas. This led to missed diagnosis of bone marrow involvement which would have meant upstaging of these cases. However, PET-CT was found to be fairly sensitive in picking up bone marrow involvement in aggressive NHL. PET-CT was also found to have picked up many cases of bone marrow involvement in HL cases and lead to upstaging of these cases.

CONCLUSION

Once the diagnosis of lymphoma is established, PET-CT is recommended to be done before proceeding for bone marrow biopsy. PET-CT guided bone marrow biopsy to be taken, if required, to improve the outcome of such invasive procedure. PET-CT is recommended in making decisions regarding the involvement of bone marrow in cases of lymphoma; especially HL and aggressive NHL with bone marrow involvement to be considered in deciding the stage of disease. PET-CT should be considered as an alternative to bone marrow biopsy in inaccessible regions for detection of bone marrow involvement [30]. PET-CT can be complimentary to bone marrow biopsy in detection of bone marrow involvement by indolent NHL. Although PET is a relatively costly procedure, it is recommended because this cost outweighs the costs and risks associated with unnecessary surgical exploration. Further studies are recommended with larger sample size to establish the feasibility of replacing invasive and often unreliable BMB in the initial staging of HL and aggressive NHL.

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