FDG PET/CT Diagnostic Performance in Bone Marrow Involvement in Pediatric Lymphoma Patients

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ABSTRACT:

FDG PET/ CT has major role in staging of lymphoma. FDG PET/CT was recently evaluated as a supplementary lymphoma staging method for BM involvement in several studies. In the current study we attempted to evaluate the diagnostic performance of F-18 FDG PET/CT in the detection of bone marrow infiltration. This study included: 140 consecutive pediatric lymphoma patients (113 HD, 27 NHL) were investigated at initial presentation by FDG PET/CT. Follow up for a period ranged from 6-65 months were used as a reference standard to validate the results of the current study. In the current study the overall frequency of bone marrow infiltration in pediatric lymphoma was account to 27.8. BMI was more frequent in NHL (51.85 %) compared to HD (22.1 %). Conclusion: FDG PET/CT is a valuable tool in screening bone marrow infiltration in pediatric lymphoma patients.

Keywords: Bone Marrow infiltration, PET/CT and Pediatric Lymphoma.

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INTRODUCTION:

Pediatric lymphoma represents the third common malignancy in childhood [1]. Bone marrow involvement in Hodgkin's disease (HD) or aggressive non-Hodgkin's lymphoma (NHL) indicates advanced stage of disease and portends a less favorable prognosis. So many concerns about diagnosing bone marrow infiltration were present in the last few decades to identify that group who need to be submitted to more intensified therapy protocols [2]

FDG PET/CT has crucial rule in staging of lymphoma. It has the advantage of imaging of the entire soft tissue and mapping of the entire bone marrow. Abundant literature is available on value of F-18 FDG PET/CT in the evaluation of BMI in adult lymphoma patients and proved to be of high sensitivity and specificity to stratify the patient to higher risk group.

AIM OF WORK: The aim of this study was to assess the use of FDG PET/CT in evaluation of extent of BMI in pediatric lymphoma patients.

PATIENTS AND METHODS:

This Retrospective study included 140 pediatric patients, from the periods of first February, 2010 and 31 of December, 2015. All patients were referred to our Nuclear Medicine department in the initial pre-therapy phase. All patients had histopathologically proven lymphoma.

Clinical information were extracted from the medical records, including age, sex, methods of diagnosis, detailed pathology, and imaging findings.

Inclusion criteria: Pediatric patients (age < 18 years), pathologically proved lymphoma at different stages of management and Whole body FDG PET/CT.

Exclusion criteria: Adults (age >18 years), double primary, previous chemo- or radiotherapy and recent surgical intervention for bone lesion.

All patients were informed about details of the study. The ethical committee of NEMROCK and the radiation safety committee at NCI had given approval for study design.

FDG PET/CT:

Patient Preparation: Parent's instructed that their children should fast for at least 4–6 h before the study (to maintain low glucose and low insulin levels), but drink water to maintain good hydration except if sedation is indicated. The fasting blood glucose level was determined. The preferred fasting blood glucose is below 150 mg/dl.

Acquisition: FDG PET/CT study was done using a dedicated PET/CT scanner (Biograph, True-Point; Siemens). This camera integrates a PET scanner with a dual-section helical CT scanner (40 slice Emotion; Siemens) and allows the acquisition of co-registered CT and PET images in one session. Scanning started 45 - 60 min after tracer injection of 5–10 MBq/kg, or 0.15–0.30 mCi/kg, with a minimum dose of 37 MBq (1 mCi). Intravenous contrast agent was administered in most patients. Initially, patients were examined in the supine position with arms elevated, and CT scanning was started with the following parameters: 400 mAs; 120 kV; slice thickness, 3 mm; pitch, 1.5. The CT scans were acquired during normal respiration from skull vault reached caudally to the mid thighs. PET was performed immediately after acquisition of the CT images (5–7 bed positions; acquisition time, 2-3 min/bed position). The CT-data were used for attenuation correction, and images were reconstructed as 3-mm slices applying a standard iterative algorithm (ordered-subset expectation maximization).

When necessary, sedation was used in accordance with guidelines before 18F-FDG PET/CT imaging to ensure patient immobilization and adequate image quality.

Processing: Images were interpreted at a workstation equipped with fusion software (advantage Window AW, Siemens) that provides multi-planar reformatted images and enables display of the PET images, CT images, and fused PET/CT images was interpreted by 2 experienced nuclear medicine physicians. The analysis was conducted on per patient and per lesion based analysis.

Imaging Interpretation:

Qualitative (Visual) assessment: For 18F-FDG PET/CT interpretation, any focal or patchy inhomogeneous uptake, superior-to hepatic reference in the bone marrow was interpreted as abnormal FDG uptake, the CT images were revised for corresponding CT changes.

Quantitative assessment: The maximum standardized uptake values (max SUV) were recorded for the most active osseous lesion in each patient after manual application of the volumetric regions of interest on the trans-axial attenuation-corrected PET slices, around the areas demonstrating the greatest accumulation of 18F-FDG and away from any nearby overlapping activity. Another sizable ROI was drawn over the normal liver where its max SUV was considered reference activity.

Data Analysis per patient and per lesion was performed depending on the following criteria:

Two experienced nuclear medicine physicians, blinded to the result of the F-18 FDG PET/CT scan and interpreted as positive or negative for BMI

Positive PET/CT: Isolated/multiple focal uptake in the bone marrow more than the liver uptake and/or diffuse heterogeneous marrow involvement with sites of intense focal involvement with higher uptake than the liver.

Negative PET/CT: PET/CT was interpreted negative for BMI in the presence of diffuse homogenous marrow involvement with uptake less than or equal to liver. FDG PET/CT findings were correlated with available pathological reports.

The follow up data was used together with the pathological, other radiological modalities and clinical data as a reference standard to differentiate between the false positive results of PET/CT and false negative results of BMB regarding BM infiltration.

Statistical Analysis

Data was analyzed using SPSS win statistical package version 21 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data, comparison between two groups was done using either student t-test or Mann-Whitney test (non-parametric t-test) as appropriate. A p-value ≤ 0.05 was considered significant. Receiver operator characteristic (ROC) curve analysis used to find the best cut off value for SUV max to discriminate between progression & regression status as measure of prognosis with response, with the highest sensitivity & specificity. The cut off value for SUV max was correlated with pathological types using Chi-square test. A p-value < 0.05 was considered significant. P value was set significant at 0.05 level [3].

RESULTS:

Clinico-pathological Characteristics:

This retrospective study was conducted on 140 pediatric patients with a biopsy proven lymphoma. Their main clinico-pathological characteristics are given in table (1).

Table (1): Clinico-pathological characteristics in pediatric lymphoma patients (n =140).

Clinical data	HD (N = 113)		NHL (N=27)	
Age:				
Median (range)	9 (3-17)		7 (2-16)	
Sex:				
Male No. (%)	85 (75.22%)		20 (74.1%)	
Female No. (%)	28 (24.78%)		7 (25.9 %)	
Male: Female	3:1		2.9 :1	
Pathological	**Nodular sclerosis**	80 (70.8 %)	**Diffuse large B cell**	7 (25.9 %)
subtypes:	**Mixed cellularity**	27 (23.9 %)	**Burkitt's**	15 (55.6 %)
No. (%)	**Lymphocyte rich**	4 (3.5 %)	**Anapl. large T cell**	4 (14.8 %)
	Lymphoc depletion	2 (1.8 %)	**B-cell lymphoblastic**	1 (3.7 %)
Initial staging				
I	13 (11.5 %)		0 (0 %)	
II	51 (45 %)		9 (33 %)	
III	22 (19.5 %)		4 (15 %)	
IV	27 (24 %)		14 (52 %)	
B symptoms				
Present	29 (25.7 %)		4 (15 %)	
Absent	84 (74.3 %)		23 (85 %)	

Bone marrow infiltration in FDG PET/CT:

Based on PET/CT results; Positive bone marrow infiltration was seen in 41 patients (27 HD & 14 NHL). Regional based data analysis was used to evaluate the extent & burden of BM infiltration all over the skeleton using PET/CT. The skeleton was divided into 8 segments: Spine 2, pelvis 2, skull 1, long bones 1, ribs 1 & scapula, clavicles, sternum1. The commonest site of involvement of bone marrow is seen in pelvis and spine representing 27.3% and 26.3% respectively (figure 1).

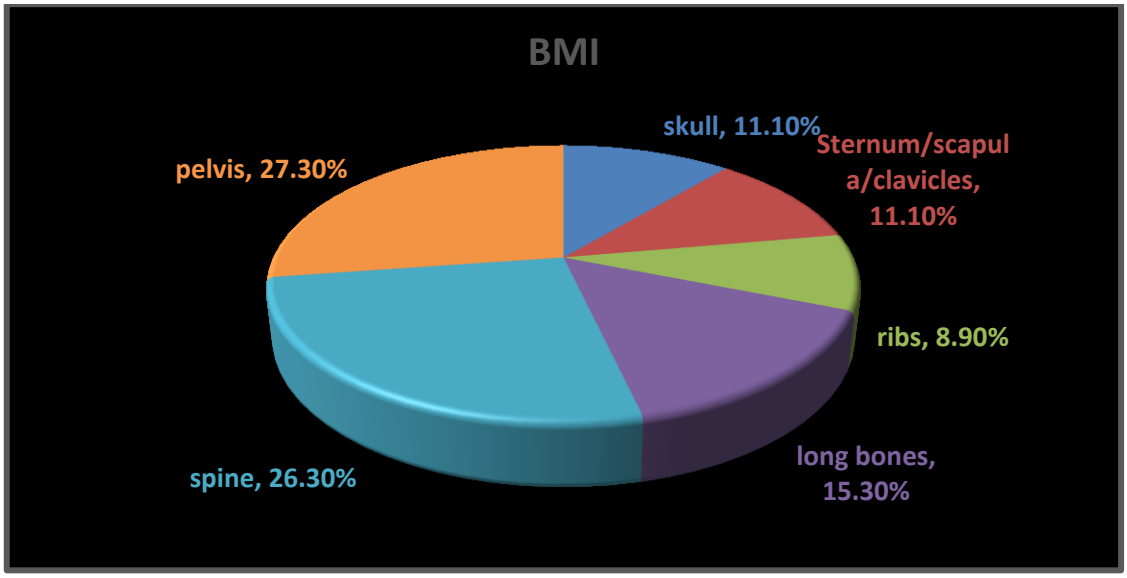

Figure (1): Regional distribution of bone infiltration in different skeletal sites using PET/CT (n. of sites = 190).

Bone marrow involvement based on the fore mentioned 5 point scoring system was assessed. The majority of the enrolled patients (70.7 %) were scored I with negative BM infiltration. Where the rest of patients had positive marrow infiltration (29.3 %) and scored from 2 to 5 according to tumor load in the following descending pattern, score 5 (9.3 %), score 4 (9%), score 2 (6%) & score 3(5%).

The pattern analysis of bone marrow infiltrative lymphoma lesions in PET/CT showed focal marrow lymphomatous infiltrative lesions in 26 patients (63.4 %) that were significantly higher than the diffuse pattern which was presented in 15 patients (36.6 %) ($P<0.05$). Moreover associated morphological CT changes (mainly cortical) were seen in 46.3 % of patient.

Clinico-pathological & follow up results:

Clinico follow up data using various laboratories and radiological imaging results were used to confirm presence or absence of BM infiltration as well as monitoring therapy response. Accordingly BM infiltration was confirmed in 39 patients {14 biopsy proven, 19 combined PET and radiological CT changes, while the remaining 6 patients were proved during follow up}. On the other hand 101 patients were free of bone marrow infiltration all-through the duration of the study. A significantly higher frequency of positive bone marrow infiltration was demonstrated in NHL 14/27 patients (51.9%) compared to 25/113 patients (22.1 %) in HD (P value 0.06).

Significantly higher frequency for negative compared to positive marrow infiltration PET/CT scan results in HD patients. On the other hand no significant difference between the number of positive & negative marrow infiltration in PET/CT results was demonstrated in NHL. No false negative PET/CT scan results were demonstrated in both groups with high sensitivity indices (sensitivity & NPV) that mount to 100%.On the other hand two false positive instances with marrow infiltration PET/CT results were seen only in HD group. No false positive PET/CT results were recorded in NHL group Therefore a non-significant decrease in specificity indices (specificity, PPV) and total accuracy were demonstrated in HD (97.7% , 92.6% and 98.2%) compared to NHL patients respectively (100% , 100% and 100%).(Table 2)

Table (2): Overall PET/ CT results of bone marrow infiltration in pediatric lymphoma patients: (n =140).

Modalities	HD (n=113)	NHL (n=27)
True positive	25	14
False positive	2	0
True negative	86	13
False negative	0	0
Sensitivity	100%	100 %
Specificity	97.7 %	100 %
Total accuracy	98.2%	100 %
Positive predictive value	92.6 %	100 %
Negative predictive value	100 %	100 %

A comparison between mean values of SUV max for lymphomatous bone marrow infiltrative lesions in HD with Mean SUV ±SD = 5.2 ±3.4 versus 6.9 ± 3.4 in NHL lymphoma patients revealed no significant difference in the mean values of SUV max in both groups (P=0.13).

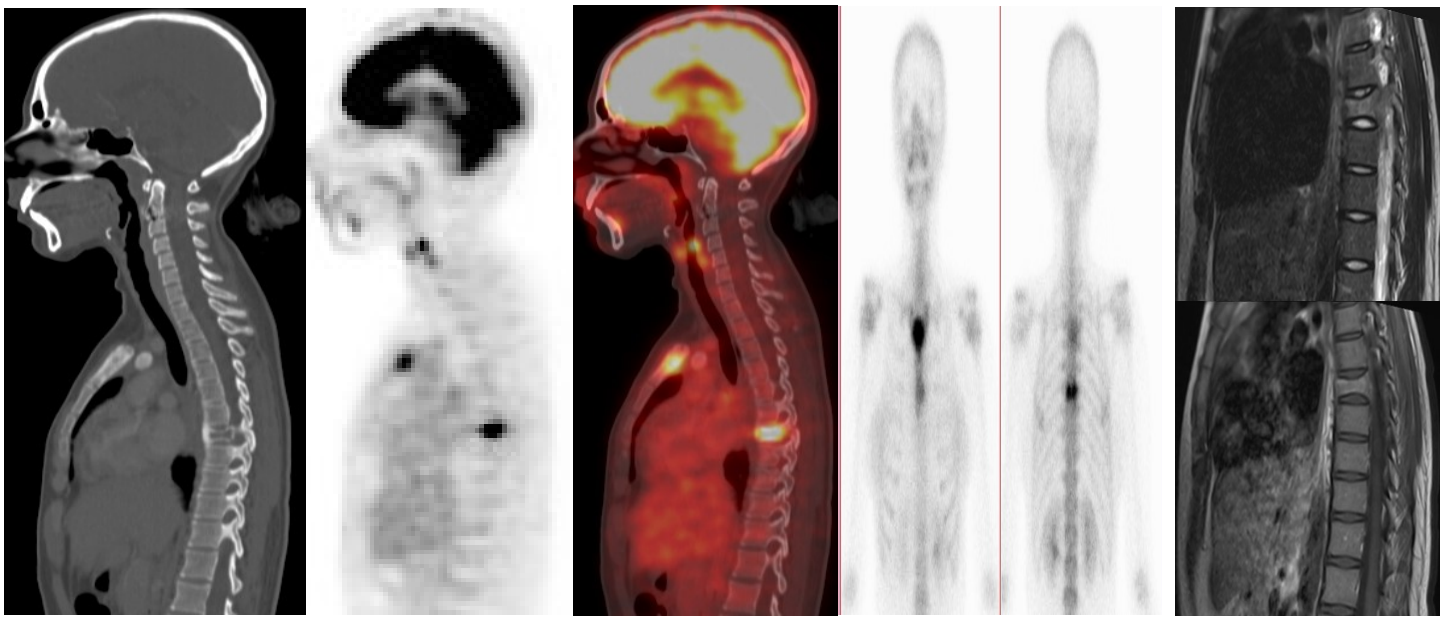

Figure (4): Initial pretreatment PET/CT revealed metabolically active FDG avid osseous infiltrate at DV7 and manubrium sterni.; Bone scan images revealed two active osseous lesions at DV7 and manubrium sterni. ; MRI spine TI and T2 sagittal images: confirmed DV7 infiltration.

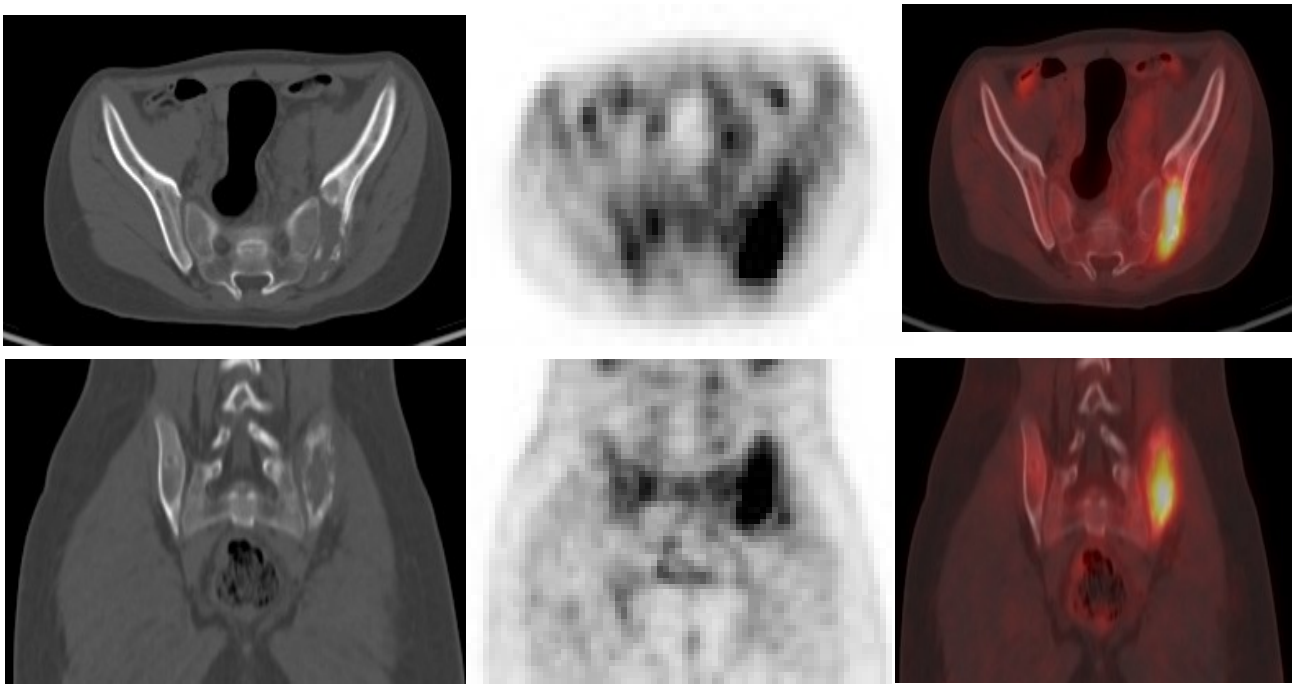

Figure (5): Initial pretreatment PET/CT revealed metabolically solitary active FDG avid destructive osseous lesion at the left iliac bone.

DISCUSSION:

Lymphoma is a common malignancy in the pediatric group. Bone marrow infiltration may have a special interest because of the added significant morbidity & upstaging disease to stage IV and more frequent relapse that may necessitate intensified therapy protocol. Therefore accurate diagnostic procedure is required for early detection and assessment of the extent of bone marrow infiltration as well as proper monitoring of therapy response [4] .

The role of FDG PET/CT in lymphoma is growing and currently its use in lymphoma patient is widely accepted in different phases of disease with high degree of accuracy particularly in FDG avid lymphoma subtypes. Several experimental & clinical data showed positive correlation between FDG uptake level, glucose transporters, metabolic activity as well as cellular proliferation & mitotic index. Moreover the introduction of hybrid imaging technique PET/CT escalating the sensitivity & specificity of FDG results in lymphoma.

FDG PET/CT possesses the ability to noninvasively demonstrate multiple sites of BM and soft tissue involvement. It is known that lymphomas are solid tumors with much higher incidence of focal or multifocal BM involvement over diffuse infiltration [5], [6] ,which has an adverse impact on histological evaluation of BM malignancies [7], [8].

In the current study; we evaluate the role of FDG PET/CT in assessment of BM infiltration in pediatric lymphoma patients.

In the current study the overall frequency of bone marrow infiltration in pediatric lymphoma was 27.8 % with more frequency of BM infiltration in NHL (51.85 %) compared to HD (22.1 %).

Similar data was reported by. **Cheng. *et al.*** [2] in 2011 , he investigated the frequency of BM infiltration in 54 pediatric lymphoma patients. The overall incidence of bone marrow infiltration was 24%. Moreover more frequent BM infiltration was demonstrated among NHL (9/23 i.e. 39.1%) compared to HD (4/31 i.e. 12.9%). Another study done by **Agrawal. *et al*** [4] **2013**, was done to assess the frequency of BM lymphomatous infiltration in 38 pediatric HD patients. BM infiltration was demonstrated in 8 patients (21.1 %).

In the present study 39 out of 140 patients have positively infiltrated bone marrow. FDG PET/CT successfully identifies those patients with marrow infiltration with no false negative FDG PET/CT results were obtained giving high sensitivity indices (i.e. sensitivity & NPV) mounting to 100%.

Other studies investigated the role of FDG PET/ CT in the detection of bone marrow infiltration in each pathological type of lymphoma separately , these studies shows that FDG PET/CT has significant higher sensitivity with diagnostic accuracy in the detection of bone marrow infiltration than that of BMB in both HD and NHL [9] , [10].

Many studies achieved that FDG PET is highly specific (specificity of 91–100%) for detection of BM involvement by lymphoma and has 100% PPV for BM involvement as confirmed by post FDG PET/CT biopsy [11], [12], [13].

PET/CT quantitative indices especially SUV max may play a role as a prognostic indicator & therapy response monitoring in assessment of lymphoma patient. The values of SUV max may reflect the proliferative and metabolic activity of lymphoma lesions. Moreover the values of SUVs before, during &/or after therapy may help in therapy planning protocols in lymphoma patients. The higher values of SUV max the more worse are the prognosis and vice versa. However, a cut off point for the SUV max values that discriminate between favorable & unfavorable prognosis in lymphoma patient is not achieved yet with few published data concerning this values.

In the current study a value of 6.85 cut off point for SUV max for BMI lesions was demonstrated as a prognostic discriminator indices. The values of SUV max higher than 6.8 have less favorable therapy response and vice versa.

Similar finding has been demonstrated by **Liang.** ***et al.***[14]. They demonstrated 8.6 as prognostic cut of value for BMI lesions in FDG PET/CT in lymphoma patients. Among PET/CT BMI positive patients, patients with SUV max of bone marrow infiltrate more than 8.6 were significantly associated with worse event-free survival and overall survival.

The extent of BMI may influence morbidity & mortality in many malignancies in pediatric patients. In the current work 5 point scoring system was used for extent assessment of BMI and to test its prognostic value in pediatric lymphoma patients. In respect to extent of BMI, significantly higher frequency of Focal BM infiltration demonstrated in 63.4 % of patient compared to diffuse BMI (% 36.6) with significant difference ($P<0.05$).

CONCLUSION:

FDG PET/CT is a reliable diagnostic tool that provides whole BM mapping essential in assessment of BMI in pediatric lymphoma patients. So it should be considered in evaluation of BMI.

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