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Role of PET/CT in the Detection of Bone Marrow Infiltration 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 role of F-18 FDG PET/CT in the detection of bone marrow infiltration and its prognostic value in respect to therapy outcome, overall survival & relapse free survival. This study included: 140 consecutive pediatric lymphoma patients (113 HD, 27 NHL) who were investigated at initial presentation by FDG PET/CT. Follow up for a periods ranging from 6-65 months were used as a reference standard to validate the results of the current study. The overall frequency of bone marrow infiltration (BMI) in pediatric lymphoma was account to 27.8%. BMI was more frequent in NHL (51.85 %) compared to HD (22.1 %). The overall survival and relapse free survival were assessed in pediatric lymphoma patient with positive & negative FDG PET-CT for BMI. No significant statistical difference in 2 years overall survival were demonstrated between the patients with positive & negative FDG PET CT bone marrow infiltration (94.3 % and 92.9 % respectively; p=0.44). Quantitative analysis of the SUV max of the bone marrow infiltrate in FDG PET/CT in respect to the therapy outcome of the studied patient's upfront SUV max value of 6.8 as a prognostic cut off value to discriminate between favorable and unfavorable therapy outcome. **Conclusions:** PET/CT has major role in lymphoma staging especially in diagnosis of bone marrow infiltration. Also, no significant difference in relapse survival in patients with of negative or positive bone marrow infiltration.

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. There remains concerns about diagnosing bone marrow infiltration (BMI) the last few decades, especially in identifying the patient 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. However, the prognostic value of FDG PET/CT detected bone marrow infiltration in pediatric lymphoma patient and whether it affect the therapy outcome and patient survival or not is not clearly identified [(3)].

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 and its Influence on therapy outcome, as well as its predictive value in respect to overall and disease free survival rates.

MATERIALS AND METHODS:

This Retrospective study included 140 pediatric patients represented at National Cancer Institute (NCI) and Children's Cancer Hospital Egypt (CCHE), between the periods of first February, 2010 and 31 of December, 2014. All patients were referred to Nuclear Medicine departments 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, imaging findings, response to treatment and survival data.

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.

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 and preferred to be 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, 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 ^{18}F-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 ^{18}F-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 region of interest (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 ^{18}F-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 liver uptake.

FDG PET/CT findings were correlated with available pathological reports.

Assessment of therapy response: Was performed based on clinical and radiological data using the **Lugano criteria** for assessment on FDG PET/CT for response assessment. With progressive disease being new or increased adenopathy or new extra nodal lymphoma [(4)].

PET Response Criteria: Response assessment with FDG PET/CT is based on metabolic activity, indicated by FDG uptake. The SUV serves as a marker of metabolic activity, and response assessment is now based on visual assessment of FDG uptake and categorized according to the "five-point scale." The five-point scale incorporates the **Deauville criteria** initially proposed for assessment on interim FDG PET/CT images [(5)]. Four categories of response have been outlined as follows:

(a) **Complete metabolic response**—score of 1, 2, or 3.

(b) **Partial metabolic response**—score of 4 or 5 with reduced FDG uptake.

(c) **No metabolic response**—score of 4 or 5 without significant change in FDG uptake.

(d) **Progressive metabolic disease**—score of 4 or 5 with increased FDG uptake or with new lesions.

In interpreting the five-point scale, a score of 1 or 2 is interpreted as negative for lymphoma, while a score of 4 or 5 is considered positive. A score of 3 likely also represents complete metabolic response at interim with resulting good prognosis and is therefore usually also considered as negative.

Relapse: appearance of new FDG avid lesions after attaining complete metabolic response.

Follow up:

Follow up data for patients were retrieved from their medical records at the hospital where clinical and radiological data and were obtained to evaluate patients' response to therapy till the last visit.

End of treatment response and follow up PET/CT was performed for 138 patients at different time scales ranging from 2 to 15 months.

The follow up data was used together with 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.

Assessment of Survival:

- **Relapse free survival:** period between attainment of complete remission and occurrence of relapse.
- **Overall survival:** the period from beginning of treatment until death or a clinical follow up.

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. Kaplan-Meier method calculated all survival estimates. Other predictor and prognostic variables were related to survival using log rank test. P value was set significant at 0.05 level.

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 subtypes: **No. (%)**	**Nodular sclerosis** **Mixed cellularity** **Lymphocyte rich** **Lymphocytic depletion**	80 (70.8 %) 27 (23.9 %) 4 (3.5 %) 2 (1.8 %)	**Diffuse large B cell** **Burkitt's Lymphoma** **Anapl. large T cell** **B-cell lymphoblastic**	7 (25.9 %) 15 (55.6 %) 4 (14.8 %) 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 in 190 sites is seen in pelvis and spine representing 27.3% and 26.3% respectively ***(figure 1)***.

Accordingly 5 point scoring system was used for assessment of BM infiltration burden:

1: No BM infiltration.

2: Any single lesion out of spine or pelvis.

3:- 2 lesions outside (spine or pelvis) or single lesion in pelvis or spine.

4:- 2 or more lesions including spinal or pelvic lesion or more than 2 lesions elsewhere

5: Extensive bone marrow infiltration.

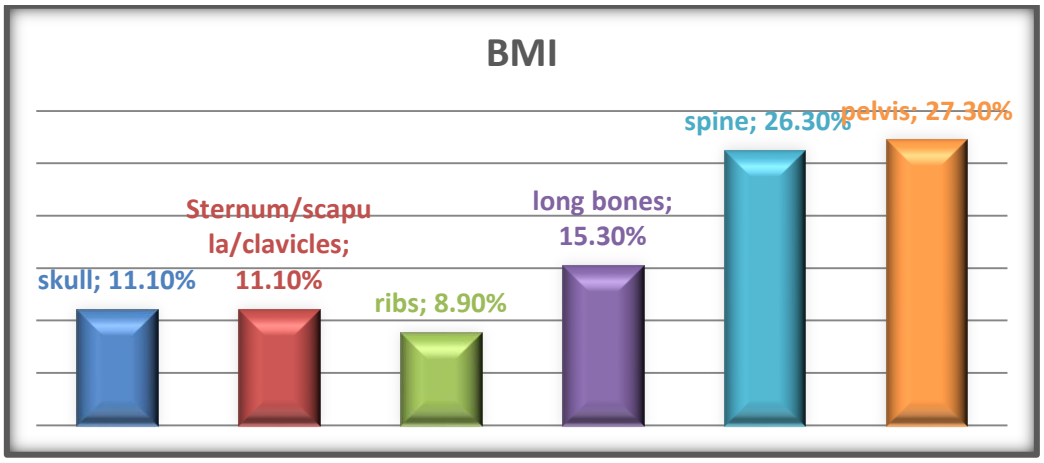


Figure (1): Regional distribution of bone marrow infiltration in different skeletal sites using PET/CT (n. of sites = 190)**.**

Bone marrow involvement based on the 5 point scoring system was assessed in 190 sites of involvement. 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%). ***Fig (2, 3)*** showed two patients with BM infiltration score 2, 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.

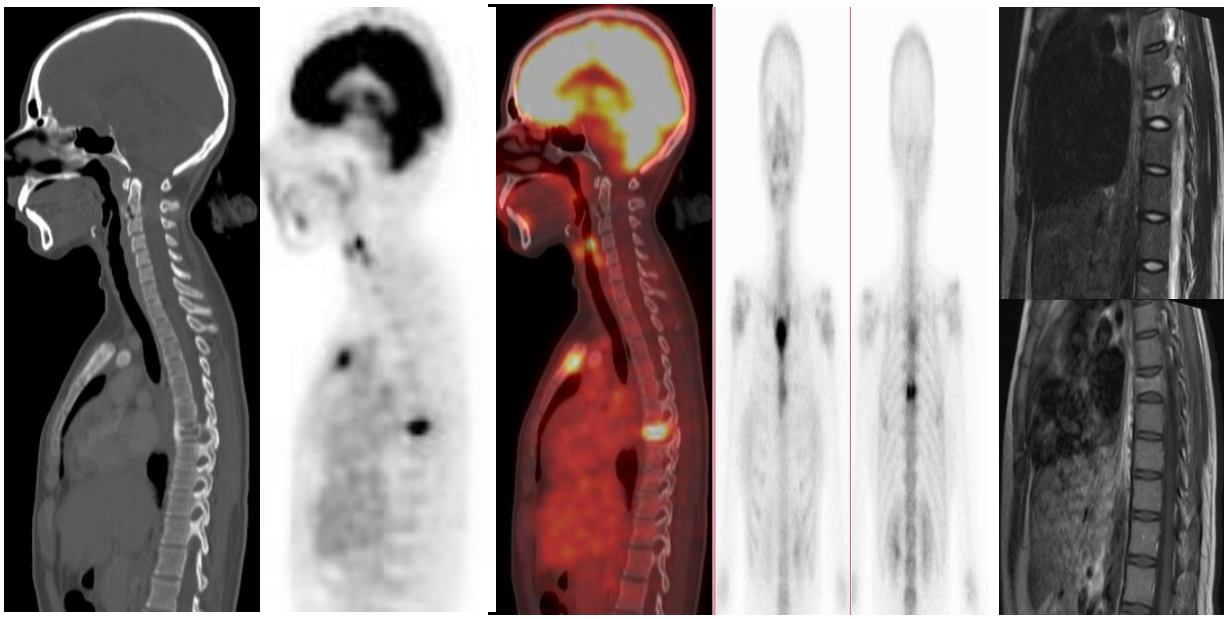


Figure (2): Initial pretreatment PET/CT revealed metabolically active FDG avid osseous infiltrate at DV7 and manubrium sterni.; Bone scan images revealed two active osseous lesions at DV7 and manubrium sterni. ; MRI spine TI and T2 sagittal images: confirmed DV7 infiltration.

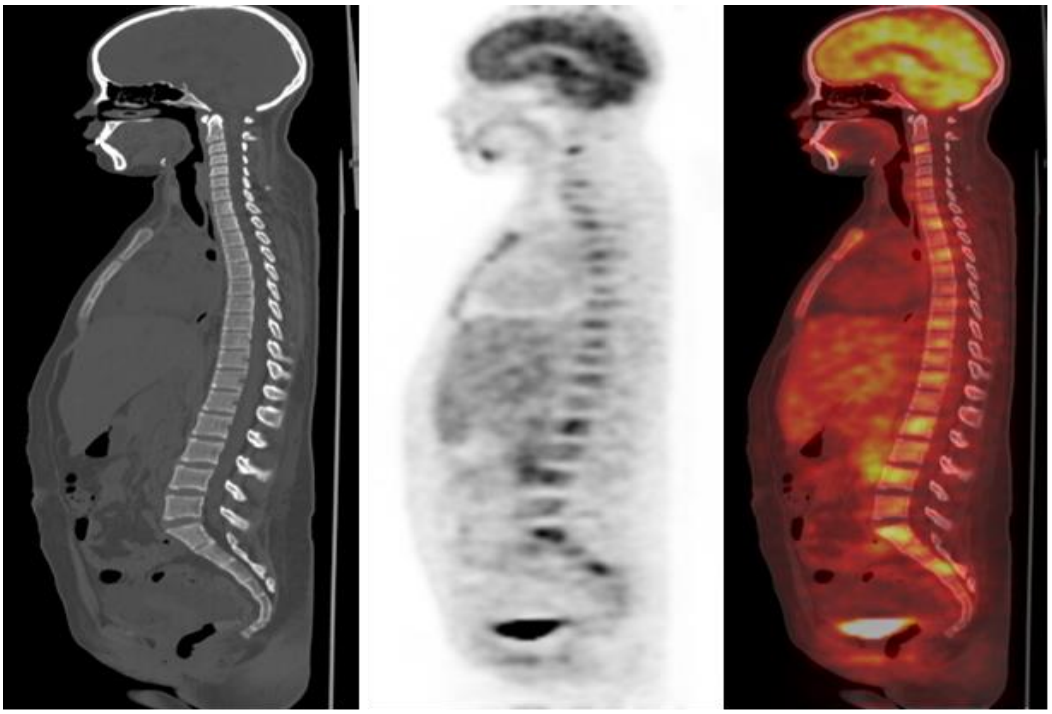


Figure (3): Initial pretreatment PET/CT revealed metabolically multiple active FDG avid lesions in bone marrow.

Clinico-pathological & follow up results: Clinical follow up data using various laboratories and radiological imaging results were used to confirm presence or absence of BMI as well as monitoring therapy response. Accordingly BMI was confirmed in 39 patients {14 biopsy proven, 19 combined PET and radiological CT changes or MRI, 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 and 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).

Survival analysis: A follow up period ranged from 6-65 months (mean = 17.14± 9.87 months) at 6 months interval was used to assess the overall survival and relapse free survival. The overall survival rate after the initial 6 months achieve 98.6 % ± 0.010 patients that drops to 93.3 % ± 0.028 after 2 years. Similarly the recorded relapse free survival rate at initial 6 months was 96.2 % ± 0.017 that reduced to 91.9 % ± 0.034 after 2 year.

No significant difference was demonstrated in overall survival rate at the initial 6 months and after 2 years in respect to presence or absence of bone marrow infiltration (P value 0.44). In the BM infiltration positive group at 6 months the overall survival was 97.6 % ± 0.024 that slightly reduced to 94.3 % ± 0.04 after 2 years. Also in bone marrow infiltration negative group no significant difference was recorded between 6 months (99 % ± 0.01) & 2 years (92.9 % ± 0.036) overall free survival ***(Figure 4)***.

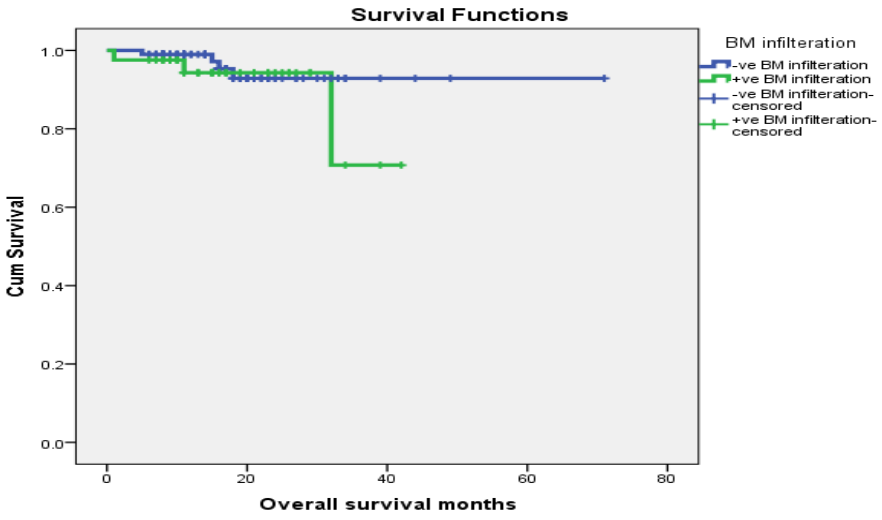
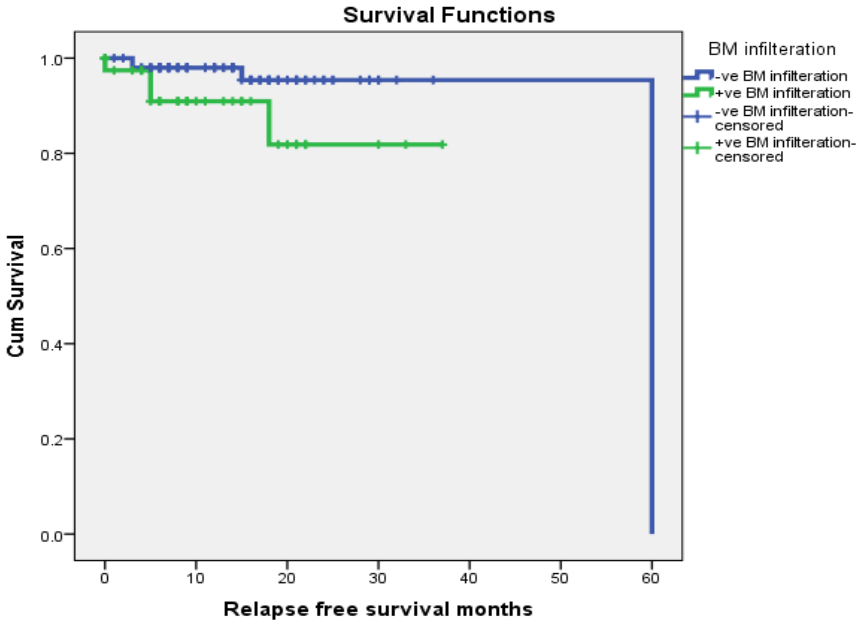
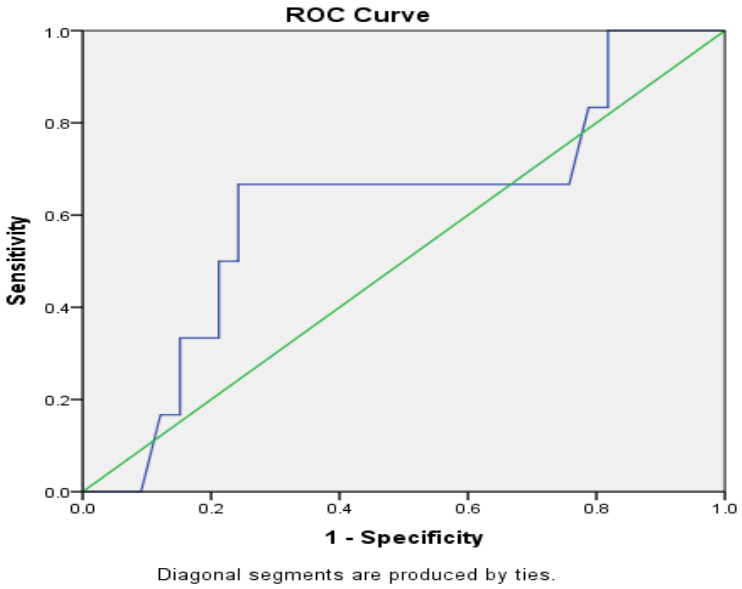


Figure (4): Overall Survival in negative and positive bone marrow infiltration pediatric lymphoma patients [n=140].

A significant difference was demonstrated in relapse free survival rate in the initial 6 months and after 2 years in respect to presence or absence of bone marrow infiltration (P<0.05). In the BMI positive group the 6 months relapse free survival was 90.9 % ± 0.05 that significantly reduced to 81.8 % ± 0.097 after 2 years. In the BMI negative group the 6 months relapse free survival was 98 % ± 0.014 that slightly reduced to (95.4 % ± 0.029) at 2 years follow up with no significant statistical difference ***(Figure 5)***.



ROC curve was used to mark a prognostic SUV max cut off point that discriminate between progressive & regressive course of disease following therapy in positively marrow infiltrated pediatric lymphoma patients with best compromise between sensitivity & specificity. ROC curve marked SUV max of 6.85 as a prognostic cut-off discriminator between both groups with a sensitivity of 66.7%, and specificity of 75.8% ***(Figure 6)***.



Predictive value of PET/CT in terms of Tumor burden: Correlation between prognosis and BM tumor burden via the 5 point scoring analysis is done. Only 6 /101 of patients with score one showed an unfavorable prognosis. Though 6 out of 39 with bone marrow infiltration has unfavorable prognosis, the magnitude of tumor burden in BMI group seems to have no significant impact in respect to prognosis ***(Table 3)***.

Table (3): Relation between PET/CT Scoring of bone marrow involvement and response to treatment in pediatric lymphoma (n=140):

score	Response to treatment		Total	P value
	Regressive (PR +CR)	Progressive (Relapse +progression)		
1	95 (94.1%)	6 (5.9%)	101(100%)	0.06
2	7 (77.8%)	2 (22.2%)	9 (100%)	
3	5 (100.0%)	2 (0%)	7 (100.0%)	
4	12 (100.0%)	0 (0%)	12 (100.0%)	
5	9 (81.8%)	2 (18.2%)	11 (100%)	
Total	(84.6%)	(15.4%)	140 (100.0%)	

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 [6].

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 [7, 8], which has an adverse impact on histological evaluation of BM malignancies [9, 10].

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] . They 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 patient i.e. 39.1%) compared to HD (4/31 patient i.e. 12.9%). Another study done by ***Agrawal. et al*** [6], was done to assess the frequency of BM lymphomatous infiltration in 38 pediatric HD patients with 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 mounting to 100%.

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 FDG PET/CT [12, 13 and 14].

There is limited debatable data in the literature regarding the prognostic value of positive FDG PET/CT for BMI in pediatric lymphoma in respect to therapy response & outcome. Moreover therapy adapted protocol considering results of FDG PET/CT in evaluation of BM infiltration in pediatric lymphoma. In this work, both overall survival and relapse free survival were assessed in pediatric lymphoma patients with positive & negative FDG PET/CT for BMI.

No significant statistical difference in 2 years overall survival were demonstrated between the patients with positive & negative FDG PET/CT bone marrow infiltration (94.3 % and 92.9 % respectively; p=0.44).

This result was matched with Hong, et al. [15] study which include 89 patients with diffuse large B-cell lymphoma (DLBCL), they found no significant differences in 2

years overall and recent free survival in patients with positive or negative bone marrow infiltration findings on FDG PET/CT (59.4% vs. 78.0% respectively).

On contrary to our results; ***Liang, et al***. [16] showed a significant difference in his study between PET/CT positive and PET/CT negative patients for BMI regarding overall survival. They stated that the 3 years overall survival was higher in the patients with negative PET/CT for BMI than that with PET/CT BMI positive (84.2%±6.5% vs. 44.1%±8.6%; P=0.003). The fore mentioned debatable results can be explained on the basis of the difference in the selected population& therapy protocol as well as the overall limited frequency of deaths in the initial 2 years after therapy in pediatric lymphoma patients [16].

Our results revealed significant statistical difference between FDG PET/CT positive & negative BMI results in respect to 2 years relapse free survival (81.8 % ± 0.097 vs. 95.4 % ± 0.029; P<0.05).

Similar finding has been achieved by ***Berthet, et al.*** [3] in NHL patients with DLBC type who concluded the independency of FDG PET/CT bone Marrow status as a predictor of relapse-free survival.

In respect to HD, ***Purz, et al*** [17] make a comparison between a positive & Negative BMI by PET in 175 HD patients in respect to relapse free survival (EFS). They showed a trend towards a worse prognosis, if BM is positive.

However, because of the overall low rate of events, the difference in the results is not statistically significant ($P > 0.05$).

Despite of the contradict of the published data regarding the overall prognostic value of FDG PET/CT in respect to BMI in pediatric lymphoma patients, there is a more tendency toward unfavorable prognosis in positive BMI PET/CT patients, however further large more homogenous studies are needed to achieve solid conclusive results for validation in clinical practice.

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 [18].

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.*** [16]. 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 in the present study significantly higher frequency of Focal BM infiltration demonstrated in 63.4 % of patient compared to diffuse BMI (% 36.6) with significant difference ($P<0.05$).

Moreover, no significant difference was demonstrated in therapy outcome between patient with focal & extensive BMI in the current work. This finding can be explained on the heterogeneity of selected population, variation in risk scoring and therapy regimen as well as favorable outcome especially with modern therapy protocols.

On the other hand, BM infiltration may follow all or none rule in respect to prognosis in pediatric lymphoma patients i.e. Single focal BMI lesion may have similar outcome to extensive marrow infiltration. However, further larger study with more homogenous group of patient may be required for clarifying such finding.

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. Also, there is no significant difference in relapse free survival in patients with negative BMI as compared with positive BMI.

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