Original Paper, Oncology

FDG-PET/CT in Early Assessment of Response to Therapy in Pediatric Hodgkin Lymphoma

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ABSTRACT:

Purpose of the study: was to estimate the value of early assessment of response in pediatric Hodgkin lymphoma (PHL) patients using FDG-PET/CT. **Methods:** prospective analysis of 195 patients presented in Children's Cancer Hospital, Egypt (CCHE) with pathologically proven untreated PHL, they underwent ^{18}F-fluorodeoxyglucose positron emission tomography (F-18 FDG PET/CT) early after 2 cycles of chemotherapy (PET 2).This chemotherapy regimen consists of concurrent treatment with Adriamycin, Bleomycin ,Vinblastine & Dacarbazine (ABVD). Analysis of PET 2 was done according to the Deauville score (5-point score) with cut-off 3-4 between Minimal Residual Uptake (MRU) and positive result. **Results:** Follow-up was done for mean period of 2.9 years (range, 0.6 to 5.2 years).Visual assessment of PET 2 was found to be significantly correlated with Overall Survival (OS) and Progression Free Survival (PFS) in advanced stages PHL (intermediate and high risk patients); the estimate for OS and PFS was 83.3% and 68.8 respectively in the PET-positive (PET +ve) group compared with 97.3% and 92.6|% respectively in the PET-negative (PET – ve) group (p-value <0.0001 and 0.0001). **Conclusion:** Early assessment of FDG-PET/CT after 2 cycles of ABVD in PHL shows potential value in prediction of OS and PFS in advanced stages (intermediate and high risk patients).

Key words: FDG-PET/CT, pediatric HL, prognosis.

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INTRODUCTION:

Malignant pediatric lymphomas account for approximately one-third of all childhood cancers where PHL represents 40% of this entity and it comprises 6% of all childhood cancers worldwide[1]. In Egypt, childhood lymphomas represent 1.3% of all incident cancers and 28.7% of all childhood cancers occupying the second rank among all childhood malignancies; PHL representing 36.4% of this entity[2]**.** Survival outcomes depend on the rapidity with which the response to treatment occurs; it was noticed that most patients who have lymphoma and who achieve complete remission (CR) have achieved therapy response after 2–4 chemotherapy cycles. In fact, the kinetic of the metabolic response during the first cycle of chemotherapy has been found to be prognostic[3]. The conventional anatomic imaging for treatment response monitoring is based on reduction in tumor size on CT, which is not an accurate early predictor of outcome[4], however, functional assessment of response using early F-18 FDG PET/CT in adults has been demonstrated to predict therapy outcome at an earlier stage of treatment,[5]. A systematic review in 2009 concluded that for advanced stage HL, F-18 FDG PET performed after a 2-4 cycles of standard chemotherapy seems to be a reliable prognostic test to identify poor responders[6]. The 1st international workshop on interim PET in lymphoma held in 2009 proposed the first criteria for qualitative interpretation of interim F-18 FDG PET (Deauville criteria)[7]. Deauville criteria propose simple reproducible rules for qualitative interpretation of interim PET interpretation in malignant lymphomas[8]**.**

AIM OF THE WORK:

To evaluate the potential prognostic role of early assessment of response to therapy in F-18 FDG PET/CT performed after two cycles of ABVD **(PET2)** in PHL patients with different risk stages using the Deauville criteria.

PATIENTS AND METHODS:

Patients and study design:

A total of newly diagnosed 195 patients with biopsy proven PHL, presented in CCHE, between July, 2007 till March, 2012 and met the inclusion criteria were enrolled in the study. The study was approved by the hospital review board, and written informed consent was obtained from all patients and/or parents. Inclusion criteria were as follows: newly diagnosed patients between 1 and 18 years old with biopsy proven PHL, receiving their first chance of treatment, and have performed F-18 FDG PET/CT after two cycles of ABVD with or without initial baseline PET study. We excluded patients younger than 1 year or older than 18 years old, patients with relapsing lymphoma and patients with life threatening impairment of organ function or diabetes mellitus. Data from these patients were prospectively collected and analyzed, early PET/CT results did not influence the scheduled first-line therapeutic strategy. All patients underwent conventional tumor staging procedures at baseline including history taking, clinical examination and routine pre-treatment investigations. Disease stage was established according to the "Ann Arbor staging system"[9]**.** The patients were sub-divided into three risk groups according to the presence or absence of adverse disease features and clinical "B" symptoms. The patients are treated according to the hospital protocol

(NCI.CU-HD.IV/ABVD-2002) in respect of their risk group. Low risk group patients were treated with 4 cycles of ABVD and Involved Field Radiation Therapy (IFRH), intermediate risk group patients were treated with 6 cycles of ABVD with or without IFRTH, and high risk group patients were treated with 8 cycles of ABVD. ABVD chemotherapy was administered to all the subjects at standard doses on an outpatient basis. All patients were re-staged at the end of therapy according to the revised response criteria for malignant lymphoma by the International Harmonization Project[10]. Patients were followed till September 2012 (the time of analysis) or until radiologic and/or histopathologic evidence of disease progression, relapse or death giving median follow-up of 2.8 years, mean 2.9 (range, 0.6 to 4.3 years). Biopsy was done to confirm active disease either at the end of first-line treatment or relapse during the period of follow-up. All patients with confirmed active HL after first-line therapy were transferred to further therapy, which consisted of high-dose chemotherapy with or without autologus stem cell therapy (ASCT), or conventional chemotherapy or consolidative radiotherapy according to the hospital protocols.

FDG-PET/CT imaging:

Patients underwent F-18 FDG PET/CT after two cycles of ABVD as late as possible before administration of the next cycle with a minimum interval of 10 days. ^{18}F-FDG was produced from an on-site cyclotron and chemistry facility. Whole-body F-18 FDG PET/CT Imaging was performed using three-dimensional acquisition on an advance 40 slices PET/CT scanner with True-X imaging reconstruction software (Siemens Biograph® True Point™). Sedation was used in most of the patients. After at least 4 h. of fasting; patients received an intra-venous injection of 5.55 MBq/kg (0.15 mCi/kg) body-weight dose of ^{18}F-FDG (minimum dose, 74 MBq (2 mCi); maximum dose, 555 MBq (15 mCi) after checking finger-stick blood glucose level (should be ≤ 160 mg %) using commonly available portable monitoring devices. Acquisition was started after 45 to 60 min period of uptake. Whole-body PET scan was acquired in overlapping bed positions in the same axial coverage as CT scan, with a 2-min acquisition per each bed position. Attenuation-corrected PET images were reconstructed with an ordered-subset expectation maximization iterative reconstruction algorithm. CT was performed as low–dose CT for attenuation correction and anatomical localization from the mid thighs to the base of the skull with the arm extended above the head. Intravenous contrast media was given in all studies. An initial scout image was obtained with 35 mAs and 120 kVp for attenuation correction- low dose CT, this was followed by a spiral CT at 0.5 s. per rotation with exposure factors 60 mAs (quality reference) and 120 kVp, a reconstructed slice thickness of 5mm and an increment of 3 mm . The whole body effective dose from the low dose CT was on average 3.4 mSv.

FDG-PET/CT interpretation:

PET, CT, and fused PET/CT images were digitally archived and exported to dedicated workstations, using the imaging standard—'Digital Imaging and Communications in Medicine' (DICOM). The program converts the intensity values automatically to SUV. F-18 FDG PET/CT

was interpreted by a consensus of 2 experienced observers who were unaware of clinical, radiologic, and follow-up data. Initial pre-treatment F-18 FDG PET/CT was available for comparison. According to the recommendations of Deauville criteria[7]**;** FDG-PET/CT were identified as; **PET 2–ve :** if no pathological increased ^{18}F-FDG uptake at any site, including all sites of previously increased pathologic uptake or with uptake less than or equal to MBPS (criteria '1' and '2') **PET 2 +ve :** in the presence of focal ^{18}F-FDG uptake which is moderately increased than the liver or markedly increased at any site and/or new lesions and could not be attributed to physiologic bio-distribution, benign uptake or normal anatomy (criteria '4' and '5'). **PET2-MRU:** when ^{18}F-FDG uptake is higher than the mediastinum, but lower than or equal to the liver were classified as (criterion '3').

Statistical analysis:

Descriptive statistics such as mean, median and range were used to describe baseline demographic and clinical profile of all patients' data. For the study of the prognostic effect of PET 2, PFS and OS were chosen as endpoints. Data were considered at other causes of death or if the patients were alive free of progression/relapse at last follow-up. The OS and PFS results were calculated by the actuarial method of Kaplan and Meier and then compared using the log-rank test for equality of survivor functions[11]. The prognostic significance of the variables (age, gender, stage, risk group and visual analysis of early PET) was assessed by uni-variate. Differences between groups were analyzed using the log rank test (p value). All data analyses were performed using the statistical software package SPSS 18.0 (SPSS Inc., Chicago, IL). All tests were 2-sided with a p value of less than 0.05 used to indicate statistical significance[12]**.**

RESULTS:

Patients' outcome:

195 pediatric patients were followed till September 2012 (the time of analysis) or until radiologic and/or histo-pathologic evidence of disease progression, relapse or death giving median follow-up of 2.8 years, mean 2.9 (range, 0.6 to 4.3 years). 176 patients (90.3 %) had maintained a continuous complete remission (CCR) after a median follow-up of 2.5 years, 3 patients (1.5%) experienced treatment failure and 16 patients (8.2%) relapsed after a median period of 1.5 years. 6 patients died after a median follow-up of 1.4 years; half of them died after experiencing treatment failure and the other half after relapse. The patients who relapsed were shifted to 2nd line of therapy and autologus stem cell therapy (ASCT). We did not observe any non-cancer deaths (for instance, deaths unrelated to Hodgkin lymploma or its treatment) as the first event. Out of the 195 PET 2 scans, 166 (85.1%) scans were considered as PET 2 -VE **(**figure 1), 24 (12.3%) scans as PET 2 +VE **(**figure 2), and 5 (2.6%) scans as PET 2 -MRU**.** Among the166 patients with a PET 2 -VE scan; 152 patients were still in CCR and 13 patients achieved a CR but relapsed later on with death encountered in 2 of them. In the 24 patients with PET2+VE scan; 18 of these patients maintained CCR after first-line treatment. 3 patients in this group achieved a CR but relapsed

later on and one of them died and 3 patients experienced treatment failure and subsequently they died. No events were encountered in the PET2-MRU group and the 5 patients achieved CR at the end of therapy and they maintained CCR throughout the duration of the study. Therefore, this group of patient was considered as PET2-ve during the analysis**. The patient's characteristics and the outcome in relation to results of visual assessment of PET 2 are listed in Table 1.**

Table (1): Demographic details of the studied patients in relation to interim PET- visual interpretation

Characteristic	Interim PET	
	Positive	**Negative**
Number of patients	24	171
Male/female	17/7	128/43
Mean age(years)	8.7	9.5
Pathology:		
MC-CHL	11	85
NS-CHL	10	71
NLR-CHL	0	0
LD-CHL	1	0
NLPHL	2	9
Stage:		
1	2	4
2	11	90
3	4	40
4	7	19
Risk:		
Low	9	92
Intermediate	5	40
High	10	39
Therapy:		
4ABVD	0	21
4ABVD+IFRTH	8	66
6ABVD	2	18
6ABVD+IFRTH	4	27
8ABVD	10	37
8ABVD	0	2
Outcome:		
CCR	17	159
TTT failure	3	12
Relapse	4	0

Survival analysis:

OS and PFS in the different risk group in relation to qualitative assessment of PET 2: The effect of the results of qualitative assessment of PET 2 in the different risk groups on OS and PFS are shown in Table 2. Fig. (1) showed patient with good respond to therapy (PET-ve) and Fig.(2) showed residreal disease following 2 cycles of chemotherapy (PET+ve).

No statistically significant correlation was found between OS and PFS in low risk group of patients, while they are significantly correlated with the intermediate and the high risk groups. The Kaplan-Meier survival curves of the risk group and the qualitative assessment of PET 2 are represented in Figures 3 and 4.

Univariate analysis:

We studied **the effects** of **the clinical factors** such as the gender, pathological sub-type, clinical stage and risk group as well as visual assessment of PET 2 **on OS and PFS**. We found that the risk group and the visual assessment of PET 2 are significantly correlated with OS and PFS, while the other clinical factors were not. The rates of OS and PFS and the p- values are shown in **Table 3.**

Table (2): OS, PFS in relation to visual assessment of PET 2 in the different risk group

Parameter	Cumulative OS%	p-value	Cumulative PFS%	p value
Gender				
Male	97.2%	0.65	89.4%	0.97
Female	90.5%		87%	
Pathology				
M.C.	94.1%		92.4%	
N.S	98.8%	0.146	86.2%	0.8
LR	100%		83.3%	
NLP-HL	90.9%		81.6%	
Stage				
I	100%		95.8%	
II	98%	0.399	91.2%	0.17
III	89%		86.4%	
IV	95.8%		74.5%	
Risk				
Low	100%	0.025*	97.8%	<0.0001*
Intermediate	95.5%		82.9%	
High	86.6%		77%	
Visual assessment				
PET2-VE	97.3%	<0.0001*	92.6%	<0.0001*
PET2+VE	83.3%		68.8%	

(*) A statistically significant result ($p < 0.05$)

Table (3): OS, PFS in relation to the clinical parameters and PET2 results:

Parameter	Cumulative OS%	p value	Cumulative PFS%	p value
Low risk				
PET2-VE	100%	--	97.6%	0.853
PET2+VE	100%		100%	
Intermediate risk				
PET2-VE	100%	<0.0001*	88.3%	0.001*
PET2+VE	60%		40%	
High risk		0.05*		
PET2-VE	88.5%		83%	0.037*
PET2+VE	80%		46.7%	

(*) A statistically significant result ($p < 0.05$)

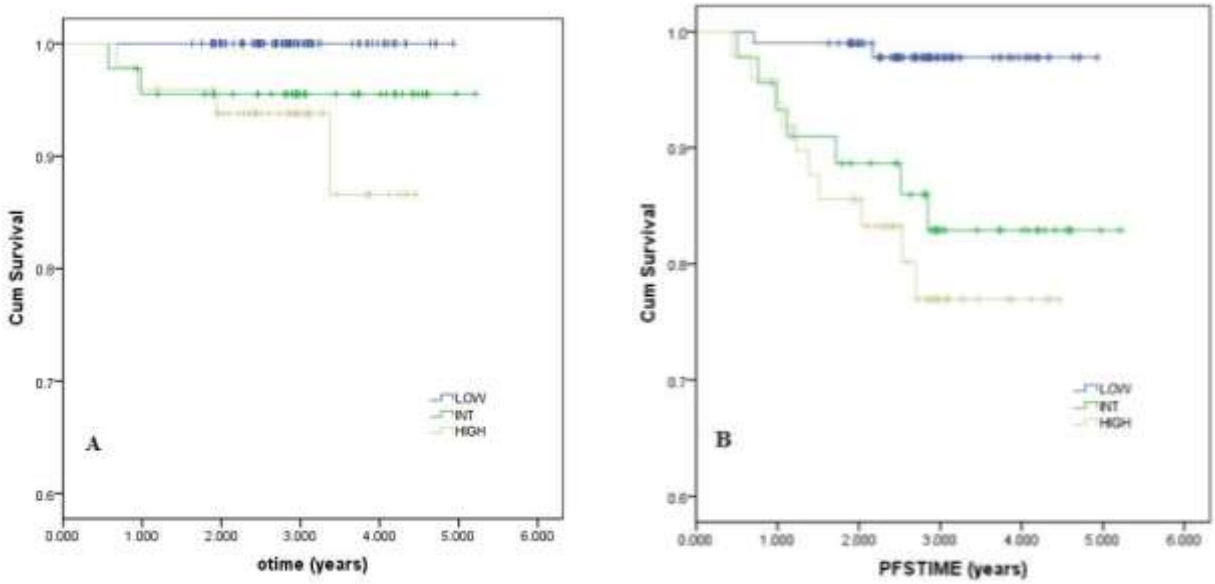

Figure (3): OS (A) and PFS (B) curves in relation to the risk group.

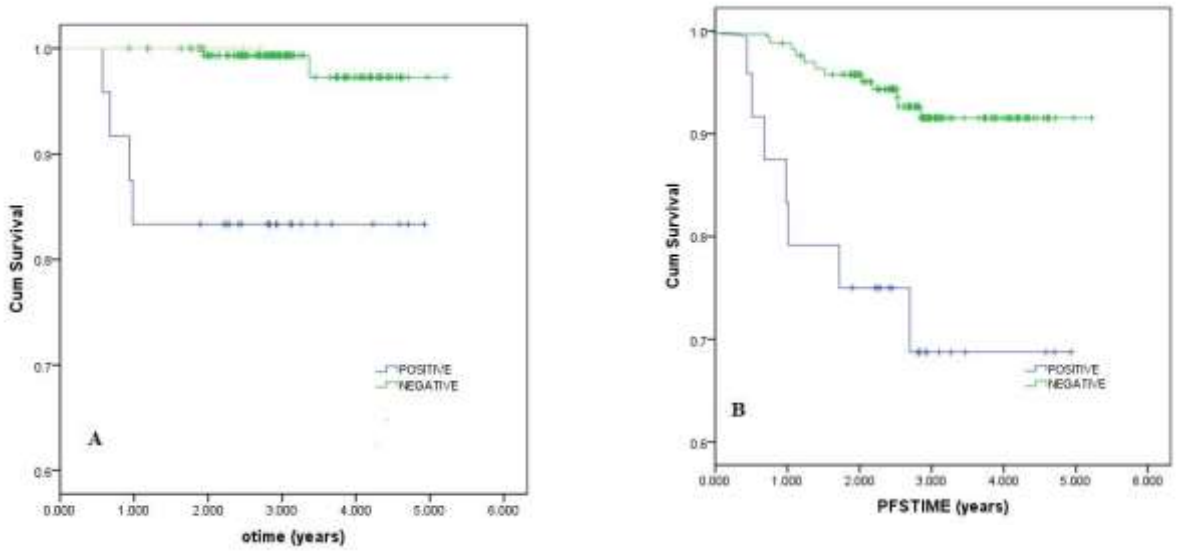

Figure (4): OS (A) and PFS (B) curves in relation to the qualitative PET results.

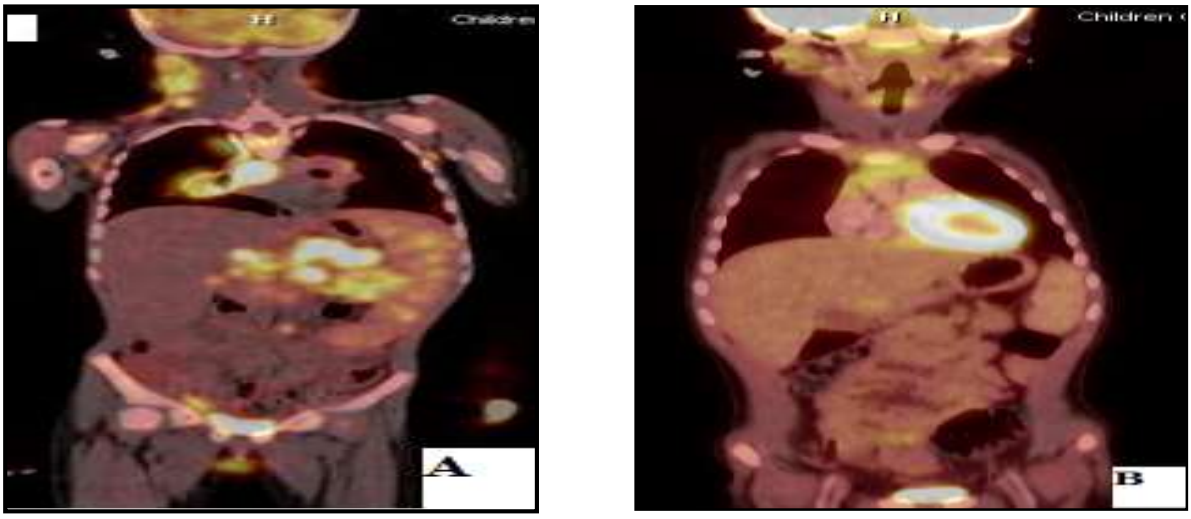

Figure 1: 5-y-old female children with CHL (NS), stage IV (A) Fused PET1 image shows multiple FDG-avid supra-diaphragmatic nodal lesions in bilateral cervical, bilateral axillary, sub-carinal, pre-vascular and right hilar nodes as well splenic and bone marrow infiltration(B) Fused PET2image: considered as negative with no pathological FDG uptake could be seen.

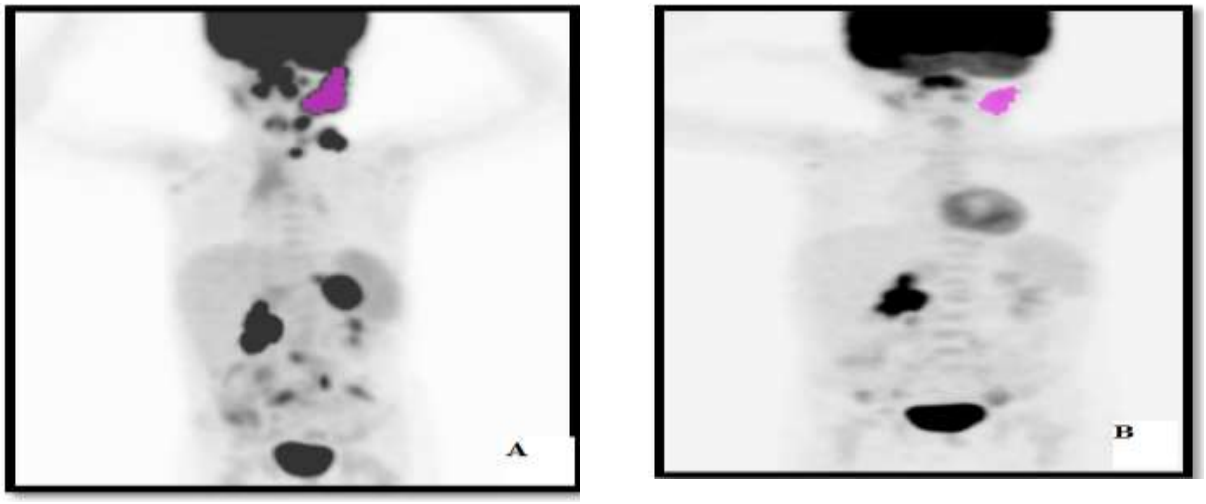

Figure 2: 4-y-old-male child, presenting with pathologically proven NLPHL, stage III.(A) PET1 image shows multiple supra- and infra-diaphragmatic lesions in multiple bilateral cervical, supra-clavicular, splenic hilar and mesenteric nodes. (B) PET2 image: considered as positive PETwith FDG uptake in multiple residual lesions noted which is moderately increased than the liver.

DISCUSSION:

Several studies in adult malignant lymphomas had shown that early assessment of response to therapy by PET/CT is as an important prognostic parameter which is useful for the identification of patients with an increased risk for relapse or progression[6]. In our population we found that the risk group is the only pre-therapeutic clinical factor predicting overall survival (OS) and progression-free survival (PFS) (P=0.025 and P<0.001) respectively. This is consistent with **Hutchings et al.,**[13,14] who analyzed the predictive value of interim PET/CT in adult HL; they showed that the presence of extra-nodal disease is an independent prognostic parameter of PFS and not clinical stage.

Visual (qualitative) analysis was done according to the recommendations of Deauville criteria using the 5-point scale score[7]**,** accordingly we identified three groups; PET2-negative (PET2-Ve), PET2-positive (PET2+VE), and PET2-minimal residual uptake (PET2-MRU), we considered MRU patients as PET2-ve for the analysis. Similarly, other studies stated that the best predictive value in HL is obtained if MRU is regarded as PET-negative **(13 and 15)**. Our results showed 166 PET2-Ve, 24 PET2+Ve and 5 PET2-MRU interim PET studies showing an excellent early response to treatment (85% negative and MRU) reflecting the chemo-sensitivity of the disease; 15% only of our patients are considered as PET2+Ve which is consistent with the percentage recorded in other literature showing that around 10% of patients undergoing early PET restaging, a persisting uptake is recorded, most often in the site where a bulky tumor was documented at baseline**(13, 16, 17)**. In the present study, positive interim PET scan is associated with higher incidence of treatment failure, relapse and /or death as 29% (7/24) of PET2+VE patients have developed treatment failure or relapse with death encountered in three of them, while only 7.2% (12/166) with PET2-Ve patients developed relapse with death encountered in only two of them. Our data also indicated that visual analysis of interim PET after two cycles of therapy can be predictive of PFS and OS, We found that the OS and PFS among patients in the whole population with negative PET2-Ve results were 97.3% and 92.6% and among those with positive PET 2 +ve results were 83.3% and 68.8% with significant difference (p<0.0001). Similar results were reported in a large retrospective study analyzing early interim FDG-PET performed in 304 Adult Hodgkin lymphoma (AHL) patients with both early and advanced stages, they found the 9-year OS and PFS among the 251 patients with a negative PET2 scan was 98.2% and 91.7% compared with the 53 patients with a positive PET2 scan were 62.5% and 27.3% (P<0.0001)[18]**.** The lower PFS estimate in their study was attributed to the large number of patients and the longer period of follow-up.

A risk-adapted, response-based approach is the new trend in treatment of PHL**(19)**. In our study, the patients were treated according to their risk groups. Therefore, we classified the patients into three risk groups (low, intermediate and high) based on the clinical stage, and the presence of certain adverse factors.

We investigated the value of interim PET scan in prediction of OS and PFS in the three risk groups. **In the low risk group** (early stages); OS was 100% in the three groups, whereas PFS was 100%, in PET2-

VE and PET2-MRU and 97.6% in PET2+Ve (P=0.853). it was not valuable in prediction of survival in this group as no significant different between the three interim PET results due to high survival rates in this stage in our pediatric population patients.

On the other hand, in high and intermediate risk groups (advanced stages), it can predict OS and PFS; **In the intermediate risk;** the OS and PFS were 100% and 88.3% in PET2-Ve and 60% and 40 % in PET2+Ve with statistically significant differences (P=0.001 and P <0.0001 respectively). **In the high risk**; the OS and PFS were 88.5% and 83% in PET2-VE versus 80% and 46.7 % in PET 2 +VE with statistically significant differences (p=0.037and p=0.05 respectively). Most of the literature that had investigated the predictive role of interim PET in early stage HL was similar to our study as they did not report that interim PET as predictive of outcome (OS and PFS) in adult HL patients with early stages and favorable prognostic factors [20, 21].

Gallamini et al.[22] investigated the role of interim PET scan in advanced-stage adulthood HL in a large prospective study including 260 patients , they reported the 2-year PFS among patients with negative PET results was 95% and among those with positive PET results was 12.8% (p<0.0001). In this study, interim PET appeared to over-shadow the prognostic value of the international prognostic score (IPS) and emerged as the single most important tool for planning risk-adapted treatment in multivariate analyses. However, **Cerci et al.,**[15] had found in their series evaluating 104 patients with AHL that qualitative assessment of interim PET is the most important factor providing valuable prognostic information of treatment success in overall and in subgroups of HL patients with early- or advanced-stage disease, independent of the risk according to the international prognostic score (IPS). Also, **Zinzani et al.,**[18], had analyzed their series of 304 untreated AHL patients as two groups of early and advanced stage patients. In early stages; they reported 9-year OS and PFS of 100% and 94.7 among the 128 patients with a negative PET scan compared with 85.2% and 31.3%scan among the 19 patients with a positive PET (p=<0.0001 and p=0.0001 respectively). whereas, in advanced stages patients; the 9-year OS and PFS were 96.4% and % 88.6% among the 123 patients with a negative PET scan as compared with 50.5% and 28.7% scan among the 34 patients with a positive PET (p<0.0001 and p=0.0002 respectively). They explained the difference between their results and those of previous studies to their population's size and distribution, as their study was the largest cohort involving early-stage patients, and it was well balanced (147 early-stage and 157 advanced-stage patients) as well as the long follow-up period (9 years).

We did observe in four negative interim PET scans, increased FDG uptake in the lungs which was not previously affected by the disease with no other signs of activity in all other previously affected sites. Such finding was proven to be attributed to infectious/inflammatory changes in the lungs using CT, biopsy or follow-up. This finding in patients with lymphomas may be seen in interim PET scan following chemotherapy because of previous treatments in these immune-compromised patients [23]. Another finding encountered in some cases in our series is the rebound thymus hyperplasia.

The current study showed the usefulness of early PET/CT performed after 2 cycles of combined chemotherapy in assessment of pediatric Hodgkin's lymphoma (PHL) especially in the intermediate and high risk groups. The risk group and the visual interpretation of interim PET were the most important prognostic factors that show better performance in predicting OS and PFS in univariate analysis.

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