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The Value of Quantitative Analysis in Evaluation of the Prognostic Role of Interim FDG-PET/CT in Pediatric Hodgkin's Lymphoma in Egypt

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ABSTRACT:

Introduction: Positron emission tomography using ^{18}F-flurodeoxyglucose (FDG-PET) is considered an excellent tool for staging and monitoring disease status in patients with lymphoma. **Aim of the study:** To assess the prognostic role of interim ^{18}F-Fluorodeoxyglucose (^{18}F-FDG)-PET/CT in pediatric patients with Hodgkin lymphoma (PHL).**Patients and Methods:** prospective analysis of 195 patients presented in CCHE with pathologically proven pediatric HL, they underwent interim PET/CT after 2 cycles of ABVD. Semi-quantitative analysis using maximum standardized uptake value (SUV max), average SUV (SUVmean2.5 and SUVmean40%), metabolic tumor volume (MTV) measured after thresholding to a threshold SUV value of 2.5(MTV2.5) and at 40% of SUV max (MTV40%) and total lesion glycolysis (TLGs) corresponding to MTVs (TLG2.5and TLG40%). The parameters were calculated as absolute values and as percentage of difference between the initial and the interim's hottest residual lesion. Follow-up was done for period of 2.9 years (range, 0.9 to 5.2 years, Clinical outcomes were obtained from medical records. **Results:** Univariate analysis showed that the risk group, interim PET 2 and SUV mean were significant predictors for OS and PFS. (2.5) has the highest hazard ratio. In multivariate analysis, using the significant prognostic factors found in univariate analysis as covariates we found same factors are

important prognostic factor that can predict OS and PFS.

Conclusion: Assessment of early interim PET/CT after 2 cycles of ABVD in PHL shows additional potential value in prediction of OS and PFS quantitatively.

Key words: FDG-PET/CT, pediatric HL, Early response, prognosis, interim PET, MTV, TLG.

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INTRODUCTION:

Malignant pediatric lymphomas account for approximately one-third of all childhood cancers. Pediatric Hodgkin lymphoma (PHL) represents 40% of this entity and it comprises 6% of all childhood cancers worldwide ***[1].***In Egypt, childhood lymphomas incidence represent 1.3% of all cancers and 28.7% of all childhood cancer. It ranks the second among all Childhood malignancies; PHL represents 36.4%of this entity ***[2].***Survival outcomes in PHL depend on the rapidity with which the response to treatment occurs. It was noticed that most patients who had complete remission (CR) had also achieved good therapy response after 2–4 chemotherapy (CTH) cycles. In fact, the kinetic of the metabolic response during the first few cycles of CTH has been found to be indicative of prognostic response ***[3].***Conventional anatomic imaging, based on reduction in tumor size is not an accurate early predictor of outcome ***[4].*** On the other hand functional assessment of response has been superior for predicting therapy outcome at an earlier stage of treatment ***[5].***FDG-PET/CT has rapidly evolved to become essential diagnostic tool in management of HL and as reliable marker of early assessment of tumor chemo-sensitivity ***[6].*** A systematic review published in 2009 concluded that FDG-PET/CT performed after 2 cycles of standard CTH (interim PET) found to be a reliable prognostic test to identify poor responders in advanced-stage HL***[7].***Interim FDG-PET/CT can be analyzed both qualitatively and semi-quantitatively. We published qualitative date using D eavilla criteria in 2013 [8].The maximal standardized uptake values (SUV max) and The average standardized uptake values (SUV mean) are widely accepted semi-quantitative biomarkers derived from FDG-PET/CT. they can be used in the assessment of response to first-line CTH and they proved to improve the prognostic value of interim PET ***[9].***The development of software using

automated volume- of-interest (VOI) assessments, volume-based metabolic parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) which is defined as the product of MTV and average SUV (SUV mean) have emerged as potential quantitative PET indices ***[10].*** **Aim of the work:** To evaluate the potential prognostic role of different methods of assessment of = esponse to therapy measured from interim PET (PET2) in PHL patients. We compared the different risk stages with semi-quantitative assessment using the SUV max, SUV mean, MTV and TLG.

PATIENTS AND METHODS:

Patients and study design: A total of newly diagnosed 195 patients with biopsy proven PHL, presented to the children cancer hospital Egypt (CCHE); one of the busiest clinical cancer centers in the world, between July-2007 and June-2012.All patients who met the inclusion criteria were enrolled in this prospective study. This project was approved by the hospital review board. A written informed consent was obtained from all patients guardians. Inclusion criteria were newly diagnosed patients between one and 18 years old with biopsy proven PHL, did not receive any treatment before. All performed initial FDG-PET/CT as well as interim PET after 2 cycles of CTH.

We excluded patients younger than 1 year or older than 18, 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. 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 ***[11].*** The patients were subdivided into three risk groups according to the presence or absence of adverse disease features and clinical "B" symptoms. All patients were treated according to the hospital protocol in respect of their risk group with 4- 6 cycles of ABVD with or without involved field radiotherapy (IFRTH). All patients were restaged at the end of therapy according to the revised response criteria for malignant lymphoma by the international harmonization project ***[12].***Patients were followed till December 2012 (the time of analysis) or until radiologic and/or histopathologic evidence of disease progression, relapse or death. The median follow-up was 2.8 years, mean 2.9 (range, 0.6 to 5.2 years). Biopsy was done to confirm

active disease either at the end of first-line treatment or at relapse during follow-up. All patients with confirmed active HL after first-line therapy received further therapy, which consisted of high-dose chemotherapy with or without autologous stem cell therapy (ASCT), or conventional chemotherapy or consolidative radiotherapy according to the hospital protocols.

Interim FDG-PET/CT imaging (PET2) Patients under went interim 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 from the last dose of chemotherapy.^{18}F-FDG was produced from an on-site cyclotron and chemistry facility. Whole-body 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 at time of imaging when needed. After at least 4 hours fasting; patients received an intravenous 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). Blood glucose levels were checked by the finger stick method using commonly available portable monitoring devices (should be ≤ 160 mg %).Acquisition started after 45 to 60 min relaxed waiting period of glucose uptake. An initial scout image was obtained with 35 mAs and 120 kVp. Spiral CT was performed with low–dose for attenuation correction and anatomical localization from the base of skull to the mid thighs with the arm extended above the head, 0.5 s. per rotation, 60 mAs and 120 kVp. Slices were reconstructed thickness of 5mm and an increment of 3 mm. Intravenous contrast media was given in all studies. 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-subet expectation maximization iterative reconstruction algorithm.

Interim 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 glucose intensity values automatically to SUV. The study was interpreted by a consensus of 2 experienced nuclear medicine physicians who were unaware of clinical, radiologic or follow-up data. Initial pre-treatment FDG PET/CT was available for comparison.

Semi-quantitative **analysis** SUV max, SUV mean, MTV and TLG were calculated in both

the initial and PET2-positive and PET2 Minimal residual disease MRU patients on the highest uptake lesion (leading lesion). The changes SUV max, Δ SUV mean, ΔMTV and ΔTLG were also calculated for comparison SUV max and SUV mean were calculated as the highest and average counts-per-pixel respectively and normalized to body weight ***[13].***Δ SUV max and Δ SUV mean are the percent of change in both between the initial andinterim PET ***[14].***MTV is the iso-contour connecting the outlines in the volume of interest (VOI) was set using the following approaches; Fixed SUV cut-off of 2. 5 (V2.5) and fixed threshold of 40 % of the SUV max (V40%) ***[15].***Δ MTV is calculated as the percent of change in MTV between the two PET studies. TLG was calculated by multiplying the selected PET volume (MTV) on the investigated lesions as mentioned above by the SUV mean within this volume (TLG=MTV X SUV mean). Δ TLG is calculated according to Larson-Ginsberg Index (LGI) as ΔTLG ((SUV mean) $_1$ X (Vol) $_1$ - (SUV mean) $_2$ X (Vol) $_2$/ (SUV mean) $_1$ X (Vol) $_1$ X 100***) [16]. (Fig 1).***

The following criteria are used to assess early metabolic response to therapy ***[13]; 1-*** Complete metabolic response: Complete resolution of FDG uptake. 2- Partial metabolic response :> 25% SUV max decrease after 2 cycle of treatment. 3- Stable metabolic disease: Between < 25% SUV increase and < 15% SUV max decrease. 4- Progressive metabolic disease: Greater than 25% increase in SUV max or new lesions.

Statistical analysis: PFS and OS were chosen as endpoints. They were calculated by the actuarial method of Kaplan and Meier and then compared using the log-rank test ***[17].*** The limit of statistical significance for all analyses was defined as a P value of less than or equal to 0.05. Uni-variant and multivariate analysis were done using the log rank test (p value). The limit of statistical significance for all analyses was defined as a P value of less than or equal to 0.05. Multivariate (Cox) regression analysis was used .All data analyses were performed using the statistical software package SPSS 18.0 (SPSS Inc., Chicago, IL) ***[18].***

RESULTS:

Patients' outcome: 195 pediatric patients (145 males and 50 females), mean age 9.4 years (range, 1.9 to 18.0 years) were followed till December 2012 (the time of analysis) or until radiologic and/or histopathologic evidence of disease progression, relapse or death.

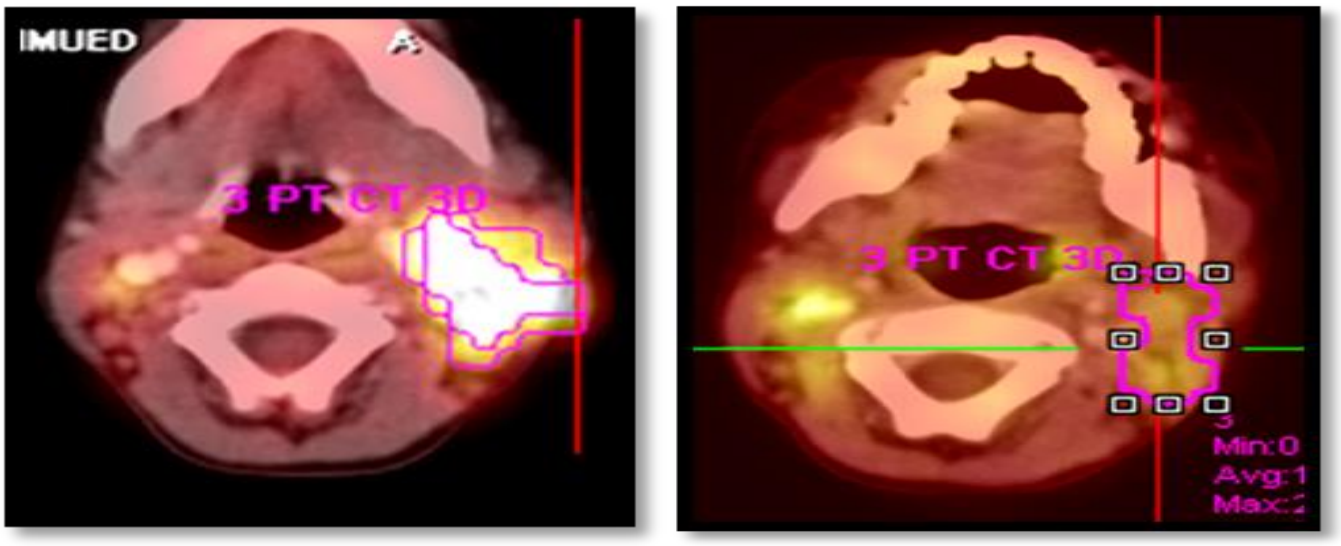
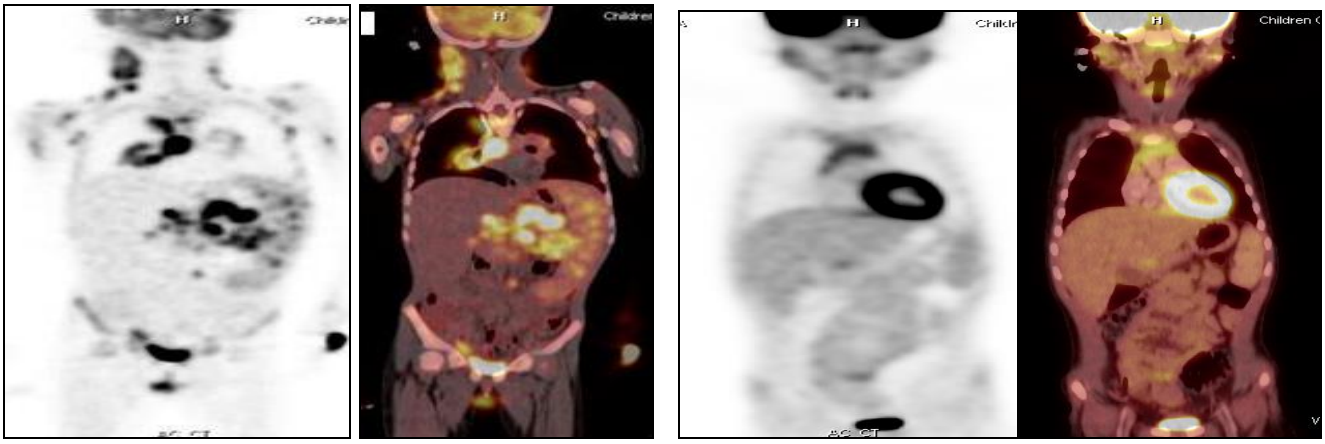


Figure 1. 4-year-old-male child, presenting NLPHL, stage III, (high risk group). On the RT: pre-therapy, fused PET/CT axial images; with large lesion in the LT cervical region. On the LT: interim PET fused PET/CT axial images; quantitative assessment of response considered positive PET 2; FDG uptake showed residual LT cervical lesion was mapped for calculation of TLG.



RT **LT**

Figure 2. 5-y-old female child with CHL (NS), stage IV (high risk group): On the RT: pre-therapy coronal PET and fused FDG-PET/CT images; showing wide spread supra-and infra-diaphragmatic metabolically active lesions. On the LT: interim PET coronal PET and fused PET/CT images; good response with negative PET2 (criterion 1); no pathological FDG uptake could be seen at any site, Rebound thymic hyperplasia is seen.

The median follow-up of is 2.8 years, mean 2.9 (range, 0.6 to 5.2 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***(Fig 2)*** **.** 6 patients died after a median follow-up of 1.4 years; 3 of them died after experiencing treatment failure and the rest after relapse. The patients who relapsed were shifted to second line of therapy and autologous stem cell therapy.We did not observe any non-cancer deaths due to other causes than HD. 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 interim PET are represented in ***(Fig 3).*****Survival analysis: OS and PFS in the different risk group in relation to qualitative assessment of interim PET. Univarate analysis**: We studied the effects of the clinical factors such as the gender, pathological sub-type, clinical stage and risk group as well as qualitative assessment of PET2 on OS and PFS. We found that the risk group and the qualitative 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 ***Figure 3.***

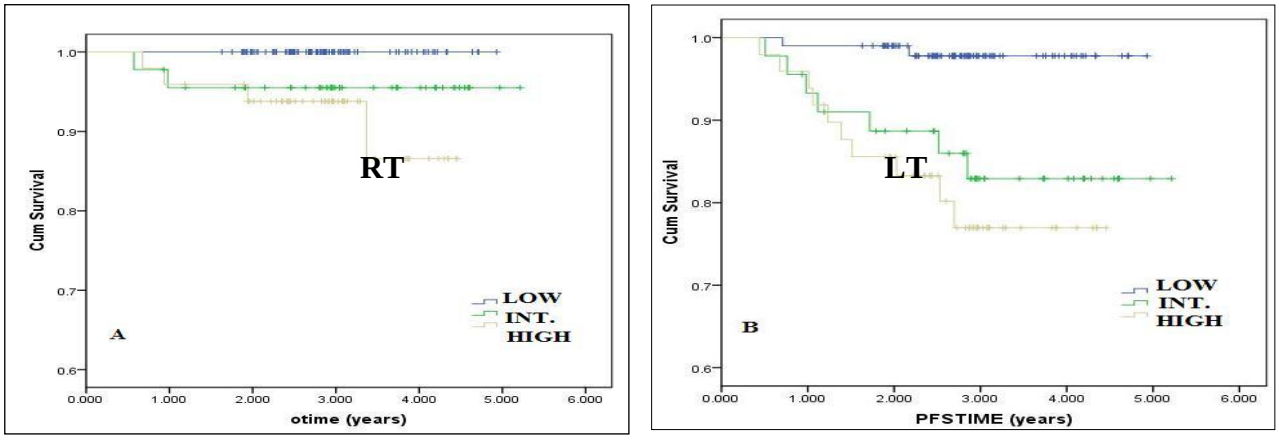


Figure (3): OS (A) and PFS (B) curves in relation to the risk group.

We also studied the effects of the semi-quantitative parameters in interim PET such as the absolute values of SUV max, SUV mean (2.5 and 40%), MTV (2.5 and 40%) and TLG (2.5 and 40%) as well as their variation in interim PET relative to pre-therapy PET on OS and PFS. Among all; Δ SUV max, SUV mean (2.5), SUV mean (40%), Δ SUV mean (40%) and ΔMTV (40%) are significantly correlated with OS and PFS. SUV max were significantly correlated only with PFS. The rates of the p and HR values are represented in ***Table 1, 2***.

Table (1): Overall survival in relation to the semi-quantitative PET parameters

Parameter	*p* value	HR	95.0% CI for Exp(B)	
			Lower	Upper
SUVmax2	0.109	1.189	0.962	1.469
ΔSUVmax	<0.0001*	1.012	1.005	1.019
SUVmean2 (2.5)	0.005*	2.013	1.232	3.291
SUVmean2 (40%)	0.039*	1.499	1.022	2.199
ΔSUVmean (2.5)	0.864	0.980	0.775	1.239
ΔSUVmean (40%)	<0.0001*	1.013	1.006	1.021
MTV2(2.5)	0.853	0.980	0.788	1.217
MTV2 (40%)	0.266	1.028	0.979	1.079
ΔMTV (2.5)	0.918	0.997	0.947	1.050
ΔMTV (40%)	0.004*	1.005	1.001	1.008
TLG2(2.5)	0.850	0.994	0.929	1.062
TLG2 (40%)	0.867	1.001	0.986	1.017
ΔTLG(2.5)	0.917	0.999	0.981	1.018
ΔTLG (40%)	0.867	1.001	0.986	1.017

(*) A statistically significant result (P < 0.05) HR: hazard ratio, CI: confidence interval

Table (2): Progression free survival in relation to the semi-quantitative PET parameters

Parameter	*p*	HR	95.0% CI for Exp(B)	
			Lower	Upper
SUVmax2	0.015*	1.176	1.032	1.339
ΔSUVmax	0.013*	0.993	0.987	0.998
SUVmean2 (2.5)	0.003*	1.604	1.179	2.181
SUVmean2 (40%)	0.022*	1.364	1.047	1.778
ΔSUVmean (2.5)	0.602	0.974	0.880	1.077
ΔSUVmean (40%)	0.016*	1.008	1.001	1.014
MTV2(2.5)	0.076	1.030	0.997	1.064
MTV2 (40%)	0.061	1.029	0.999	1.060
ΔMTV (2.5)	0.804	.995	.956	1.035
ΔMTV (40%)	0.025*	1.003	1.000	1.006
TLG2(2.5)	0.386	1.003	0.997	1.009
TLG2 (40%)	0.378	1.003	0.996	1.010
ΔTLG(2.5)	0.875	0.999	9.981	1.016
ΔTLG (40%)	0.933	1.002	0.966	1.038

(*) A statistically significant result (P < 0.05)HR: hazard ratio, CI: confidence interval

Multi-variant analysis (MVA) Multivariate analyses were done adjusted to gender and age and using the strongest predictors from the uni-variant analysis as covariates which are the risk factors, qualitative assessment of interim PET (PET2) and SUV mean(2.5); being the semi-quantitative parameter that has the highest hazard ratio (HR). We found that all three factors have statistically significance correlation with OS and PFS However, SUV mean (2.5) when tested against the qualitative assessment of interim PET failed to show independent prognostic properties ***Table 3 & 4.***

Table (3): Multivariate analysis of different factor affecting overall survival.

Parameter	*p*	HR	95.0% CI for Exp(B)	
			Lower	Upper
Risk group, PET2, SUVmean2 (2.5)				
Step 1:				
Risk group	0.005*	2.413	1.296	4.495
PET2	0.985	0.966	0.028	33.600
SUVmean (2.5)	0.343	1.669	0.579	4.807
Step 2:				
Risk group	0.003*	2.480	1.363	4.513
PET2	0.003*	0.242	0.095	0.620
Step 3:				
Risk group	0.005*	2.414	1.299	4.489
SUVmean (2.5)	0.001*	1.685	1.227	2.315
Step 4:				
PET2	0.055*	0.601	0.023	15.494
SUV mean (2.5)	0.434*	1.471	0.560	3.864

(*) A statistically significant result (p < 0.05) PET 2: visual assessment of interim PET

Table (4): Multivariate analysis of different factors affecting progression free survival.

Parameter	*p*	HR	95.0% CI for Exp(B)	
			Lower	Upper
Risk group, PET2, SUVmean2 (2.5)				
Step 1:				
Risk group	0.063	4.194	0.924	19.038
PET2	0.085	0.023	0.000	1.681
SUVmean (2.5)	0.604	0.691	0.171	2.791
Step 2:				
Risk group	0.039*	4.077	1.076	15.445
PET2	0.004*	0.082	0.015	0.456
Step 3:				
Risk group	0.055*	3.974	0.973	16.238
SUVmean (2.5)	0.008*	2.061	1.204	3.527
Step 4:				
PET2	0.052*	0.054	0.000	1.198
SUVmean (2.5)	0.606	0.713	0.197	2.576

(*) A statistically significant result (p < 0.05) PET2: visual assessment of interim PET.

DISCUSSION:

Early assessment of response to therapy by interim FDG-PET/CT is as an important prognostic parameter which is useful for the identification of patients with an increased risk for relapse or progression ***[15]***.We found in our population of 195 PHL Egyptian patients that the risk group as representation of the clinical stage and the presence of adverse factors is the only pre-therapeutic clinical factor predicting overall survival (OS) and progression-free survival (PFS) (p=0.025 and P<0.001)respectively. We analyzed the interim PET results semi- quantitatively. 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 quantitative analysis of interim PET scan in prediction of OS and PFS in the three risk groups. The results of qualitative analysis were published in 2013.

Quantitative interim PET assessment In univariante analysis (UVA) we found that semi-quantitative parameters that can be considered as important prognostic factors showing significant correlation with OS and PFS survival were the absolute values of SUVmean2 (2.5) (p=0.005 and 0.003 respectively) and SUVmean2 (40%)(p<0.0001and 0.016 respectively).They show better significant performance than the absolute value of SUV max which was correlated only with PFS (p=0.015). Though, SUV max is widely used for most of the routine work because it is an observer-independent measurement ***[19, 20].*** Some other studies had shown that SUV max was not an independent prognostic factor for survival and exhibited poor predictive performance for treatment outcomes ***[21, 22]. Sharma et al. [21]*** have analyzed initial and interim PET scans in 42 patients with pediatric lymphomas and they found no statistically significant difference in SUV max among the different outcome groups of patients (complete response and partial response groups) neither on baseline (p= 0.922) nor on early interim PET–CT (p= 0.077). This may be attributed to the calculation of the maximum voxel value as a single voxel value which may not be representative of the overall tumor uptake in a non-homogeneous tumor. This may be particularly evident in assessment of response to therapy settings as mildly active heterogeneous tumors may have a single ‘hot’ pixel that may arise from random error rather than true tumor biology and thus SUV max may not reflect the true nature of the tumor and SUV mean which is calculated by averaging

the values generated from the entire tumor may be more representative ***[22, 23].***In our study, univariante analysis also showed that the percentage of variation in interim PET/CT relative to pre-therapy scan as calculated by SUV max (ΔSUV max), SUV mean (Δ SUV mean) and MTV calculated by thresholding of 40% (ΔMTV40%) can predict OS and PFS . Also, ***Lin et al., [9]*** and ***Itti et al., [24]*** have stated the reduction in SUV might be beneficial for the assessment of response in malignant lymphomas. Several studies in multiple malignancies other than lymphomas had suggested that TLG could be a reliable and probably better quantitative index of treatment response than SUV max and MTV such as in lung cancer ***[24]***,head and neck cancer ***[22]*** and tonsillar carcinoma***[26].*** Their findings regard TLG which is a combination of SUV and MTV that represents the degree of FDG uptake multiplied by the size of metabolically active tumor is an ideal metabolic parameter of tumor burden ***[27].***Our results showed that SUV, MTV and their variation in interim PET/CT relative to pre-therapy scan (ΔSUV and ΔMTV) had predictive performance better than the TLG and ΔTLG which was not predictive of neither of OS nor PFS. Also, ***Tseng et al. [27]*** had reported in their study on 30 patients with adult HL that the changes in SUV max, SUV mean, MTV and TLG in interim PET relative to pre-therapy PET, were predictive for PFS and OS. In our study, Multivariate analysis adjusted to gender and age and using the strongest predictors from the univariante analysis as covariates which are the risk, visual assessment of interim PET (PET2) and SUV mean(2.5) being the semi-quantitative parameter having the highest hazard ratio (HR). We found that the three parameters are important prognostic factors that can predict OS and PFS. However, SUV mean (2.5) when tested against the visual assessment of interim PET failed to show independent prognostic properties, indicating that qualitative assessment is stronger than quantitative assessment ***[8].*** In the same line, several studies had shown that qualitative reading is superior or equal to quantitative evaluation in assessment of advanced adult HL ***[28].***In contrast, ***Moon et al. [26]*** have stated that their results do not guarantee that MTV is not a significant prognostic factor for overall survival as it was a significant prognostic factor with higher hazard ratio than that of TLG in univariante analysis. Moreover, it was a marginally significant prognostic factor on multivariate survival analysis. We did not measure overall tumor burden quantitatively especially in cases where there are appearance of new lesions. In these patients although there may be reduction in the quantitative parameters

calculated, however, the overall disease may be progressed and this could be a potential limitation in our study.

CONCLUSION:

This study showed the usefulness of early interim PET/CT performed after 2 cycles of CTH in assessment of PHL in the intermediate and high risk groups. . The semi-quantitative interim PET/CT parameters can be considered as important prognostic factors showing significant correlation with OS and PFS survival were Δ SUV max, SUV mean (2.5), and SUV mean (40%).

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