^{18}F-FDG PET/CT Value in Evaluation of Early Response to Treatment as a Predictor of Progression Free Survival in Patients with Pediatric Lymphomas

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بسم الله الرحمن الرحيم

" قالو سُبحانك لا علم لنا إلا ما علَّمتنا إنك أنت العليمُ الحكيم "

صدق الله العظيم

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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 adults 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 with or without baseline study, analysis of interim PET was done visually according to the Deauville score (5-point score) with cut-off 3-4 between MRU and positive result as well as semi-quantitative analysis using maximum standardized uptake value (SUVmax), 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 SUVmax (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, visual analysis and qualitative analysis of interim PET were significant predictors for OS and PFS. Among the semi-quantitative parameters, SUVmean (2.5) has the highest hazard ratio. In multivariate analysis, using the significant prognostic factors found in univariate analysis as covariates we found that the three are important prognostic factor that can predict OS and PFS. However, SUVmean (2.5) when tested against the visual assessment of interim PET failed to show independent prognostic properties.

Conclusion: assessment of early interim PET/CT after 2 cycles of ABVD in PHL shows potential value in prediction of OS and PFS both qualitatively and quantitatively, however, the qualitative assessment shows better performance than the semi-quantitative analysis.

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

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- **ABVD:** doxorubicin, bleomycin, vinblastine, and dacarbazine.
- **ABVE-PC:** doxorubicin, bleomycin, vincristine, etoposide-prednisone, cyclophosphamide.
- **AHL:** adult Hodgkin's lymphoma.
- **ALCL:** anaplastic large cell lymphoma.
- **ASCT:** autologus stem cell therapy.
- **BFM:** The Berlin-Frankfurt-Munster group.
- **CCG:** the Children's Cancer Group.
- **CCR:** continuous complete remission.
- **C-HL**: classic Hodgkin's lymphoma.
- **CIMs:** conventional imaging modalities.
- **CNS:** central nervous system.
- **COPP/ABV:** cyclophosphamide, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine.
- **CR:** complete response.
- **CRU:** complete remission unconfirmed.
- **CSF**: the cerebrospinal fluid.
- **CT:** computed tomography
- **CTH:** Chemotherapy.
- **DFOV:** display field of view.
- **DLBCL:** diffuse large B-cell lymphoma.
- **EBV:** Epstein-Barr virus.
- **EFS:** event-free survival.
- **ESR**: erythrocyte sedimentation rate.

- **FDG:** fluoro-deoxy-glucose.
- **FL:** follicular lymphoma.
- **HL:** Hodgkin lymphoma.
- **HSCT**: hematopoietic stem cell transplantation.
- **IFRT:** involved-field radiation therapy.
- **IPS:** international Prognostic Score.
- **ITP:** immune thrombocytopenia.
- **LR:** lymphocyte rich.
- **MC:** mixed cellularity.
- **MRD:** minimal residual disease.
- **MRI:** magnetic resonance imaging.
- **MRU:** minimal residual uptake.
- **MTV:** metabolic tumor volume.
- **MVA:** multivariate analysis.
- **NHL:** non-Hodgkin lymphoma.
- **NLP:** nodular lymphocyte predominance.
- **NLR:** non-linear regression.
- **NS:** nodular sclerosis
- **OS:** overall survival.
- **PCNSL:** Primary CNS lymphoma.
- **PD:** progressive disease.
- **PERCIST:** PET Response Criteria In Solid Tumors.
- **PET:** positron emission tomography.
- **PFS:** progression free survival.
- **PHL:** pediatric Hodgkin lymphoma.
- **PMBCL:** primary mediastinal B-cell lymphoma.

- **PR:** partial response.
- **PTCL:** peripheral T-cell lymphoma.
- **PVC:** partial volume corrected.
- **PVE:** partial volume effect.
- **RECIST:** Response evaluation criteria in solid tumors.
- **ROI:** region of interest.
- **RS:** Reed-Sternberg.
- **RT:** radiation therapy.
- **SD:** stable disease.
- **SUL:** SUV based on lean body mass.
- **SUV**: maximal standardized uptake value.
- **SUV_{bsa}**: SUV normalized to body surface area.
- **SUV_{bw}:** SUV based on body weight.
- **SUVmax**: maximal standardized uptake value.
- **T:** tumor.
- **TLG:** total lesion glycolysis.
- **TOPs:** therapy optimization protocols.
- **U/S:** ultra-sound.
- **UVA:** univariate analysis.
- **VOI:** volume of interest.
- **WHO:** World health organization.

INTRODUCTION

Introduction

Pediatric malignant lymphomas account for approximately one-third of all childhood cancers; they are considered the third most common group of cancers in children ***(Lennert and Feller, 1992)***.

In Egypt, childhood lymphomas represent 1.3% of all incident cancers and 28.7% of all childhood cancer occupying the first rank among all childhood malignancies; Non-Hodgkin lymphomas (NHL) was the main type of childhood lymphoma representing 63.6%. The remaining 36.4% were Pediatric Hodgkin lymphoma (pHL) ***(Triennial report of GPCR, 2007).***

Pediatric lymphomas are highly sensitive to standard chemotherapy, radiation therapy, or combined-modality therapy, with long-term event free survival rates ***(Brepoels et al., 2007)***. In order, to minimize the side effects of therapy without losing treatment efficacy, reduction of the number of chemotherapy cycles should be limited to the optimum for each individual patient. Also the use of radiation therapy should be restricted to those most likely to benefit from it. It is important to identify early non responders since they will ultimately need high-dose chemotherapy and stem cell transplantation. Therefore, the intensity of the treatment needs to be tailored to an individual patient ***(Ng et al., 2002)***.

The conventional anatomic imaging for treatment response monitoring is based on reduction in tumor size on CT. However, this is not an accurate early predictor of outcome ***(Rankin, 2001)***. Functional assessment of response using ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) in adults has been demonstrated to predict therapy outcome at an earlier stage of treatment, usually after a few initial cycles of chemotherapy ***(Dann al., 2007)***.

^{18}F-FDG-PET thus might be used as an early predictor of response allowing a risk-adapted treatment strategy ***(Kasamon et al., 2007)***.

The maximal standardized uptake (SUVmax) is a widely accepted functional biomarker derived from 18F-FDG PET/CT for several types of malignancies. It can be used in the assessment of response to first-line chemotherapy and it is proved to improve the prognostic value of early ^{18}F-FDG PET/CT when it is added to a visual analysis ***(Lin et al., 2007)***. However, several studies have reported that there is no association between SUVmax and worse prognosis ***(Allal et al., 2004)***.

Recently, with 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 (SUVmean) have become quantitative PET indices that can be used in assessment of treatment response and outcome of therapy in cancer patients ***(Xie et al., 2010).***

AIM OF THE WORK