



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

Thesis submitted for partial fulfillment of MD degree in  
Nuclear Medicine

By

**El-Shaymaa Mohamed Hany Mohamed Hussein**

Under Supervision of

**Prof. Dr. Hosna Mohamed Moustafa**

Professor of Nuclear Medicine  
Faculty of Medicine - Cairo University

**Prof. Dr. Alaa M. A. El-Haddad**

Professor of pediatric oncology  
National cancer institute  
Cairo University

**Prof. Dr. Walid Soliman Omar**

Professor of Nuclear Medicine  
National cancer institute  
Cairo University

**Faculty of Medicine  
Cairo University  
2013**

"قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ"  
صدق الله العظيم

آية (32) سورة البقرة

## ACKNOWLEDGEMENT

In all submission, I wish first of all to thank ALLAH, the most compassionate and the most merciful, I'm asking ALLAH to make this work helpful and useful.

I would like to express my deep gratitude to ***Prof. Dr. Hosna Mohamed Moustafa***, professor of nuclear medicine, faculty of medicine, Cairo University, who gave me a great deal of her valuable time in revising every item in this work, for her no words of praise are sufficient.

I would like to express my profound appreciation to ***Prof. Dr. Walid Soliman Omar***, professor of nuclear medicine, national cancer institute, Cairo University, for his valuable advice and continuous encouragement.

Many thanks to ***Prof. Dr. Alaa M. A. El-Hadad***, professor of pediatric oncology, national cancer institute, Cairo University, for giving me the privilege to work under his supervision and for his generous care and support to accomplish this work.

Also, I would like to thank ***the staff members of the nuclear medicine and the scientific research departments in the children's cancer hospital*** for helping me with my research work and providing me with the clinical and follow up data. They gave me a great opportunity to conduct my research in a warm and friendly environment.

To ***my family***, my profound love and appreciation for all what they have done for me to be what I am.

## ABSTRACT

**Introduction:** Positron emission tomography using  $^{18}\text{F}$ -fluorodeoxyglucose (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  $^{18}\text{F}$ -Fluorodeoxyglucose ( $^{18}\text{F}$ -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.

## Contents

	<b>Page</b>
<b>- Introduction</b>	<b>1</b>
<b>- Aim of the work</b>	<b>3</b>
<b>- Review of literature</b>	<b>4</b>
• <b>Epidemiology</b>	<b>4</b>
• <b>Pathology</b>	<b>7</b>
• <b>Staging</b>	<b>16</b>
• <b>Diagnostic work-up</b>	<b>20</b>
• <b>Treatment</b>	<b>25</b>
• <b>Prognosis</b>	<b>31</b>
• <b>Standard methods for assessment of response to therapy</b>	<b>35</b>
• <b>PET/CT imaging in pediatric patients</b>	<b>37</b>
• <b>Role of PET/CT in pediatric lymphomas</b>	<b>49</b>
• <b>Methods of assessment of response to therapy using FDG-PET scanning</b>	<b>55</b>
<b>- Patients and methods</b>	<b>70</b>
<b>- Results</b>	<b>86</b>
<b>- Case presentation</b>	<b>106</b>
<b>- Discussion</b>	<b>119</b>
<b>- Summary and Conclusions</b>	<b>129</b>
<b>- References</b>	<b>137</b>
<b>- Arabic summary</b>	<b>167</b>

## List of Tables

<b>Table</b>	<b>Description</b>	<b>Page</b>
<b>Table 1</b>	Ann Arbor staging classification for HL	<b>16</b>
<b>Table 2</b>	Factors affecting prognosis in pHL	<b>31</b>
<b>Table 3</b>	Factors influencing SUV determination for FDG at intended regions of interest, their undesirable effects, and associated required corrective measures	<b>64</b>
<b>Table 4</b>	Demographic details of the studied Hodgkin's lymphoma patients	<b>87</b>
<b>Table 5</b>	Demographic details of the patients in relation to interim PET- visual interpretation	<b>93</b>
<b>Table 6</b>	Summary of the semi-quantitative interim-PET parameters	<b>95</b>
<b>Table 7</b>	OS and its relation to visual assessment of interim PET in the different risk groups	<b>96</b>
<b>Table 8</b>	PFS and its relation to visual assessment of interim PET in the different risk groups	<b>97</b>
<b>Table 9</b>	OS and its relation to the clinical parameters and the visual assessment of interim PET	<b>99</b>
<b>Table 10</b>	PFS and its relation to the clinical parameters and the visual assessment of interim PET	<b>100</b>
<b>Table 11</b>	OS and its relation to the semi-quantitative PET parameters	<b>102</b>
<b>Table 12</b>	PFS and its relation to the semi-quantitative PET parameters	<b>103</b>
<b>Table 13</b>	Multivariate analyses of OS	<b>104</b>
<b>Table 14</b>	Multivariate analyses of PFS	<b>105</b>

## List of Figures

<b>Figure</b>	<b>Description</b>	<b>Page</b>
<b>Figure 1</b>	Morphologic features of the neoplastic cells in Hodgkin's lymphoma.	<b>8</b>
<b>Figure 2</b>	Anatomical regions for the staging of Hodgkin's lymphoma	<b>18</b>
<b>Figure 3</b>	Methods of thresholding for MTV calculation	<b>67</b>
<b>Figure 4</b>	Low-risk group (favorable disease)therapy protocol	<b>75</b>
<b>Figure 5</b>	Intermediate-risk group (unfavorable disease) therapy protocol	<b>76</b>
<b>Figure 6</b>	High-risk group (advanced disease) therapy protocol	<b>77</b>
<b>Figure 7</b>	Distribution of the studied patients according to gender	<b>86</b>
<b>Figure 8</b>	Distribution of the studied patients according to pathology sub-types.	<b>88</b>
<b>Figure 9</b>	Distribution of the studied patients according to the stage	<b>89</b>
<b>Figure 10</b>	Distribution of the studied patients according to the risk group	<b>89</b>
<b>Figure 11</b>	Therapy of the studied patients	<b>90</b>
<b>Figure 12</b>	The distribution of the results of qualitative assessment of interim PET	<b>92</b>
<b>Figure 13</b>	The distribution of the results of qualitative assessment of interim PET according to the outcome of the studied patients	<b>92</b>
<b>Figure 14</b>	OS and PFS curves for the entire study population	<b>94</b>

<b>Figure 15</b>	OS and PFS curves in intermediate risk group patients in relation to the visual assessment of interim PET results	<b>97</b>
<b>Figure 16</b>	OS and PFS curves in high risk group patients in relation to the visual assessment of interim PET results	<b>98</b>
<b>Figure 17</b>	OS and PFS curves in relation to the risk group	<b>101</b>
<b>Figure 18</b>	OS and PFS curves in relation to the qualitative PET results	<b>101</b>
<b>Figure 19</b>	Case 1	<b>107</b>
<b>Figure 20</b>	Case 2	<b>109</b>
<b>Figure 21</b>	Case 3	<b>111</b>
<b>Figure 22</b>	Case 4	<b>113</b>
<b>Figure 23</b>	Case 5	<b>115</b>
<b>Figure 24</b>	Case 6	<b>118</b>



## List of abbreviations

- **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:** autologous 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<sub>bsa</sub>:** SUV normalized to body surface area.
- **SUV<sub>bw</sub>:** SUV based on body weight.
- **SUV<sub>max</sub>:** 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 <sup>18</sup>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 et al., 2007*).

$^{18}\text{F}$ -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  $^{18}\text{F}$ -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  $^{18}\text{F}$ -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