



**Assessment of the Role of 18F-FDG PET CT
in Detection of Bone Marrow Infiltration in
Comparison to the Bone Marrow Aspirate
in Lymphoma Patients**

Thesis

*Submitted for Partial Fulfillment of the Master Degree in
Radio Diagnosis*

Presented by

Madonna Adel Mikhail Ghaly Youssif

M.B.B.CH.

Faculty of Medicine-Ain-Shams University

Supervised by

Prof. Dr. Aida Mohamed El Shibiny

Professor of Radiology

Faculty of Medicine-Ain-Shams University

Ass.Prof.Dr. Susan Adil Ali Abdul Rahim

Assistant Professor of Radiology

Faculty of Medicine-Ain-Shams University

*Faculty of Medicine
Ain Shams University*

2019



Acknowledgement

*First of all, all gratitude is due to **Allah** almighty for blessing this work, until it has reached its end, as a part of his generous help, throughout my life.*

*Really I can hardly find the words to express my gratitude to **Professor. Dr. Aida Mohamed El Shibiny**, for her supervision, continuous help, encouragement throughout this work and tremendous effort she has done in the meticulous revision of the whole work. It is a great honor to work under her guidance and supervision.*

*I would like also to express my sincere appreciation and gratitude to **Assistant Professor Dr. Susan Adil Ali Rahim** for her continuous directions and support throughout the whole work.*

Last but not least, I dedicate this work to my dear family, whom without their sincere support and love, pushing me forward this work would not have ever been completed.

Madonna Adel Mikhail Ghaly



List of Contents

Title	Page No.
List of Tables	i
List of Figures	ii
List of Abbreviations	v
Introduction	1
Aim of the Work.....	11
Review of Literature	
📖 Lymphoma	12
📖 Physics of PET / CT Scanners	28
📖 Bone Marrow Infiltration	76
Patients and Methods	94
Results	100
Discussion	112
Summary and Conclusion	117
References	120
Arabic Summary	

List of Tables

Table No.	Title	Page No.
Table (1):	Differences between HL and NHL	24
Table (2):	FDG uptake in various histologic subtypes of NHL and HL.....	39
Table (3):	Shows that the female (48.1%) and male (51.9%) of sex, also ranged 17-69 with mean 43.33 ± 15.09	100
Table (4):	Bone marrow biopsy findings distribution of the patients group	102
Table (5):	PET findings of bone marrow distribution of the patients.....	103
Table (6):	Comparison between PET findings and biopsy findings according to bone marrow which shows statistically significant difference between PET findings and biopsy findings according to bone marrow.....	104
Table (7):	Diagnostic Performance of PET/CT in detection of bone marrow involvement.....	106

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Ann-arbor lymphoid regions	23
Figure (2):	PET scans illustrate the classification of specific cases of NHL according to the Ann Arbor staging system.....	26
Figure (3):	Showing the Ann Arbor Staging System for Hodgkin's and Non-Hodgkin's Lymphoma.....	27
Figure (4):	Illustrative diagram of combined PET/CT scanner components	29
Figure (5):	Typical imaging protocol for combined PET/CT	31
Figure (6):	The process of positron emission and subsequent positron-electron annihilation results in two 511 keVannihilation photons emitted 180° apart	33
Figure (7):	Production of F-18	35
Figure (8):	Structure and metabolism of FDG	36
Figure (9):	Uptake of FDG. FDG is a glucose analogue that is taken up by metabolically active cells by means of facilitated transport via glucose transporters (Glut) in the cell membrane.....	37
Figure (10):	Misregistration artefact. Fused PET-CT scan....	42
Figure (11):	58-y-old man with colon cancer.....	43
Figure (12):	High-density metallic implants generate streaking artifacts and high CT numbers on CT image	44
Figure (13):	61-y-old patient with lung cancer who ingested barium for an esophagogram 1day before PET/CT scan.....	45

List of Figures (Cont...)

Fig. No.	Title	Page No.
Figure (14):	Bilateral near symmetrical increase of radiotracer uptake over the shoulder area representing brown fat.....	50
Figure (15):	Physiologic FDG uptake in the thymus in a 21-year-old woman with a history of sigmoid colon cancer	57
Figure (16):	Physiologic submandibular uptake.....	60
Figure (17):	Normal distribution of FDG	63
Figure (18):	FDG-avid postsurgical changes after lumpectomy and axillary lymph node dissection in a 60-year-old female breast cancer patient.....	65
Figure (19):	FDG-avid cavitory granulomatous lesion mimicking malignancy in a 62-year-old active smoker with a history of rheumatoid arthritis	67
Figure (20):	Normal distribution of FDG	73
Figure (21):	The different blood cells that develop in the bone marrow.....	76
Figure (22):	Showing the technique of the bone marrow biopsy taken from the dorsal portion of the iliac crest	79
Figure (23):	Coronal images are shown from three patients with different degrees of marrow uptake on PET	85
Figure (24):	PET images in a 66-year-old woman diagnosed with LPL/WM before and after therapy.....	86

List of Figures (Cont...)

Fig. No.	Title	Page No.
Figure (25):	Diffusely increased bone marrow FDG uptake	90
Figure (26):	Increased diffuse BM uptake on PET images.....	92
Figure (27):	Bone marrow involvement by diffuse large B-cell lymphoma in a 65-year-old man	93
Figure (28):	Nodular sclerosis type Hodgkin disease	93
Figure (29):	Age (years) histogram distribution of the patients group.....	101
Figure (30):	Pie chart lymphoma distribution of the patients group.....	101
Figure (31):	Bar chart between PET findings and biopsy findings according to bone marrow.....	105

List of Abbreviations

Abb.	Full term
μ map.....	Attenuation map
A_{inj}	Injected activity
A_{mea}	Measured activity
BAT.....	Brown adipose tissue
BFGF.....	Basic fibroblast growth factor
CECT.....	Contrast enhanced computed tomography
CT.....	Computed tomography
DLBCL.....	Diffuse large B-cell lymphoma
EBV.....	Ebstein barr virus
ENL.....	Extra-nodal lymphoma
FDG.....	Flouro-deoxyglucose
FL.....	Follicular lymphoma
GLUTs.....	Glucose transporters
HD.....	Hodgkin Disease
HL.....	Hodgkin lymphoma
HU.....	Housefield unit
IASLC.....	International Association for the Study of Lung Cancer
IFRT.....	Involved field radiotherapy
Kev.....	Kilo electron volt
MALT.....	Mucosa associated lymphoid tissue
mci.....	millicurie
MCL.....	Mantle cell lymphoma
Mev.....	Milli electron volt
MZL.....	Marginal zone lymphoma
NEMA.....	National Electrical Manufacturers Association
NHL.....	Non Hodgkin lymphoma
NK.....	Natural killer
PDGF.....	Platelet derived growth factor

List of Abbreviations (Cont...)

Abb.	Full term
<i>PET</i>	<i>Positron emission tomography</i>
<i>ROIMA</i>	<i>Mean activity in the region of interest</i>
<i>ROIs</i>	<i>Regions of interest</i>
<i>SUV</i>	<i>Standardized uptake value</i>
<i>TNM</i>	<i>Tumor Node Metastasis</i>
<i>VEGF</i>	<i>Vascular endothelial growth factor</i>
<i>WHO</i>	<i>World Health Organization</i>

INTRODUCTION

Lymphoma consists of over 50 histologically and biologically distinct lymphoid malignancies, classified into Hodgkin lymphoma and non-Hodgkin lymphoma (*De Angelis et al., 2014*). Lymphoma comprises a histologically heterogeneous group of cancers derived from the cells of the immune system. The hallmark of the disease is the enlargement and proliferation of lymph nodes or secondary lymphoid tissues (*Paes et al., 2010*).

Lymphoma is generally divided into two groups: Hodgkin's disease (HD) and an inhomogeneous group of conditions called non-Hodgkin's lymphoma (NHL). HD tends to involve a single nodal group and spread in a fixed pattern along the lymphatic chain, with infrequent extra lymph node involvement. NHL is a multifocal disease which often presents late with disseminated extranodal spread (*Drake et al., 2007*).

The extra nodal involvements are compromising in approximately 40% of patients. The term extra-nodal involvement refers to lymphomatous infiltration of anatomic sites other than the lymph nodes (*Paes et al., 2010*). It is due to regional spread of nodal disease or hematogenous dissemination. In decreasing order of frequency, the spleen, liver, gastrointestinal tract, pancreas, abdominal wall, genitourinary tract, Waldeyer ring, central nervous system, lung, bone, skin, adrenal, peritoneal cavity and biliary tract are

involved (*Lee et al., 2008*). Differentiation between disseminated lymph nodal disease involving an extranodal site and primary extranodal disease is challenging. Primary extranodal disease usually presents at an early stage; up to 74% in stage II (*Paes et al., 2010*).

Lymphomas are very sensitive to chemotherapy and radiotherapy. Recent developments in treatment have improved the outcome markedly and are cost-effective. Most patients with Hodgkin's disease (HD) or non-Hodgkin's lymphoma (NHL) can be treated successfully with curative intent (*Strobel et al., 2007*).

Accurate staging is critical for identifying patients with early-stage (stage I or II) lymphoma, which is treated with involved-field radiation therapy. Chemotherapy is performed in patients with more advanced stage disease (stage III or IV) (*Okada et al., 2010*). Thus accurate staging is the basis for the selection of an appropriate therapeutic approach, in order to prevent over or under treatment as well as to minimize morbidity related to the radio-chemotherapy regimens given (*Barrington et al., 2014*).

Integrated positron emission tomography (PET) and computed tomography (CT) performed with fluorine 18 (18F) fluorodeoxyglucose (FDG) is one of the functional imaging modalities used to visualize glucose metabolism in living

human tissues. It has been increasingly used in evaluation of oncology patients due to its high sensitivity in detection of malignancy before morphologic changes are evident (*Kobayashi et al., 2012*).

In the last decade, Imaging of tumor metabolism with (FDG-PET) has facilitated the identification of affected nodal and extra-nodal sites, even when CT has demonstrated no lesions. It also plays a role for more correct staging prior to treatment and post treatment follow-up (*Paes et al., 2010*).

In PET-CT systems the CT portion provides the anatomic information useful for accurate interpretation of PET signal. It also provides a map used for attenuation correction of PET images. Therefore PET-CT systems have replaced PET alone in most nuclear medicine departments. The performance of FDG PET-CT is better than the performance of FDG PET alone in oncology; however the added value might differ according to the clinical situation (*Groheux et al., 2013*). Basic knowledge of the mechanism of cancer imaging with FDG PET-CT is essential for accurate interpretation of PET-CT images (*Kobayashi et al., 2012*).

Diagnosis of bone marrow involvement in lymphoma has significant prognostic and therapeutic implications, as it upstages the disease to Ann Arbor stage IV. Bone marrow biopsy (BMB) from the iliac crest has been traditionally used for marrow evaluation. It is obtained from the dorsal portion of

the iliac crest, which is the most accessible approach for BM evaluation. However, it is an invasive operation and it yields information from a limited area. In addition, BMB may provide false-negative results if samples are atypical or the lesions are focal and may require general anaesthesia in children (*Cheng et al., 2013*).

In recent years, PET/CT has been widely used for accurate staging prior to treatment in lymphoma. It not only can detect a focal malignant bone marrow infiltration but also does not give rise to a painful experience (*Tateishi, 2013*). Moreover, it provides global information about the entire bone marrow, beyond the biopsiable areas (*Cheng et al., 2013*). Previous studies have reported the high sensitivity and accuracy of FDG-PET/CT in detecting BMI in Hodgkin lymphoma and Non-Hodgkin Lymphoma (*Weiler et al., 2014*).

AIM OF THE WORK

The aim of this study is to characterize the visual bone marrow FDG uptake pattern by PET-CT and to compare it to the bone marrow biopsy findings in patients with Hodgkin's disease (HL) or Non-Hodgkin's lymphoma (NHL) and to determine whether its sensitivity and accuracy are sufficient to render Bone Marrow Biopsy (BMB) redundant or not.

Chapter 1

LYMPHOMA

Epidemiology

Lymphoma is the most common primary hematopoietic malignancy (*Okada et al., 2010*).

Lymphoid neoplasms are broadly divided into Hodgkin disease (HD) and non-Hodgkin's lymphoma (NHL). Hodgkin lymphoma accounts for less than 1% of all cases of cancer, Non-Hodgkin lymphoma accounts for about 5% of all cases of cancer. Non-Hodgkin lymphoma is less predictable than Hodgkin disease and has a greater predilection to disseminate to extra-nodal sites with more incidence and prevalence in male (*Cheson et al., 2014*).

The hallmark of the disease is the enlargement and proliferation of lymph nodes or secondary lymphoid tissues. Although rare, both NHL and Hodgkin disease (HD) may arise from or involve almost any organ of the human body (*Okada et al., 2010*).

Etiology & Risk Factors:

The exact causes of lymphoma are not known. Several factors have been linked to an increased risk of developing lymphoma, but it is unclear what role they play in the actual development of lymphoma (*Cheson et al., 2014*).