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

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Madonna Adel Mikhail Ghaly

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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
PET	*Positron emission tomography*
ROIMA	*Mean activity in the region of interest*
ROIs	*Regions of interest*
SUV	*Standardized uptake value*
TNM	*Tumor Node Metastasis*
VEGF	*Vascular endothelial growth factor*
WHO	*World Health Organization*

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)***.