UNIVERSITI PUTRA MALAYSIA

AGREEMENT BETWEEN VARIOUS MEASUREMENTS OF STANDARDISED UPTAKE VALUE NORMALISED BY LEAN BODY MASS IN DETECTING BACKGROUND 18F-FDG ACTIVITY IN PET/CT ONCOLOGIC IMAGING

NUR HAFIZAH BINTI MOHAD AZMI

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By

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March 2018

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PET/CT Scan is a diagnostic imaging tool predominantly used in oncology cases. Standardised uptake value (SUV) is the widely accepted method to quantitatively assess lesions detected on PET/CT. There is a limitation to the utility of this method, however, as this value becomes falsely reduced in overweight patients.

Thus, we propose another quantitative method of using Standard Uptake Lean Body Mass (SUL) which can give a more consistent reading in patients having extremes of body mass index (BMI) values. As the prevalence of obesity is rising in this current decade, the utility of SUL becomes more relevant and necessary.

This study correlated SUV and SUL values using the liver as a baseline reference organ and identified the pattern of distribution across various BMIs. There have been some studies that assessed the variations of SUV and SUL in obese subjects, but there have not been any studies that analysed whether there is a significant difference in SUL in subjects who undergo contrast-enhanced PET/CT.

Interestingly, this study confirmed that SUL reading is consistent even among overweight patients and the utility of contrast media in PET/CT scans does not significantly differ from low dose non-contrast-enhanced scans.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk Ijazah Master Sains

PERSETUJUAN ANTARA BEBERAPA CARA PENGUKURAN *STANDARDISED UPTAKE LEAN BODY MASS* DALAM MENGESAN AKTIVITI *BACKGROUND* 18F-FDG DALAM KES ONKOLOGI MELIBATKAN IMBASAN PET/CT

Oleh

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Imbasan PET/CT adalah alat yang digunakan dalam kes onkologi. Nilai *Standard Uptake Value* (SUV) adalah kaedah kuantitatif yang diterima secara meluas bagi mentafsir kerosakan yang dikesan pada imbasan PET/CT. Terdapat kekurangan ke atas kaedah ini kerana ia berubah pada pesakit yang berlebihan berat badan.

Oleh itu, kami mencadangkan satu kaedah kuantitatif menggunakan *Standard Upatake Lean Body Mass* (SUL) yang memberi bacaan yang lebih konsisten terutama pesakit yang mempunyai peningkatan pada indeks jisim badan (BMI). Malahan, didapati isu obesiti semakin meningkat masa kini maka SUL menjadi lebih relevan dan diperlukan.

Kajian ini mengkaji hubung kait nilai SUV dan SUL menggunakan organ bahagian hati sebagai rujukan asas untuk mengenal pasti nilai kuantitatif bagi pesakit yang berbeza BMI. Terdapat beberapa kajian yang menilai kepelbagaian SUV dan SUL pada pesakit gemuk, tetapi tidak terdapat lagi kajian yang menganalisis sama ada terdapat perbezaan yang ketara bagi nilai SUL pada imbasan PET/CT berkontras.

Menariknya, kajian ini mengesahkan bahawa nilai bacaan SUL adalah konsisten walaupun di kalangan pesakit yang berlebihan berat badan dan obes. Penggunaan media kontras dalam imbasan PET/CT tidak memberi bacaan yang ketara daripada nilai asasnya.

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I certify that a Thesis Examination Committee has met on 16 March 2018 to conduct the final examination of Nur Hafizah binti Mohad Azmi on her thesis entitled "Agreement between Various Measurements of Standardised Uptake Value Normalised by Lean Body Mass in Detecting Background 18F-FDG Activity in PET/CT Oncologic Imaging" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

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Declaration by the graduate student

I hereby confirm that:

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF EQUATIONS

LIST OF ABBREVIATIONS

BMI	Body Mass Index
CE	Contrast-Enhanced
NCE	Non-Contrast-Enhanced
ROI	Region of Interest
VOI	Volume of Interest
FBS	Fasting blood sugar
ICC	Intra-Class Correlations
LBM	Lean Body Mass
PE	Predictive Equation
PET/CT	Positron Emission Tomography Computed Tomography
SD	Standard Deviation
SUL-CG	SUL computed generated
SUL-James/ SULPE1	SUL derived from the predictive equation for lean body mass by James et al.
SUL-Janma/ SULPE2	SUL derived from the predictive equation for lean body mass by Janmahasatian et al.
SUL	Standardised Uptake Value Normalised for Lean Body Mass
SUV	Standardised Uptake Value
SUV-CG	Standard Uptake Value Computed generated
SUVmax	Maximum Standardised Uptake Value within a tumour / lesion
SUVmean	Averaged value to Standardised Uptake Value within a tumour / lesion
18F-FDG	18 Fluorine – Fluoro-deoxy-glucose
CDNI	Centre for Diagnostic Nuclear Imaging, UPM/ Pusat Pengimejan Diagnostik Nuklear, UPM
PCMC	Prince Court Medical Centre
A	Centre A
B	Centre B
Max	Maximum
Min	Minimum

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Positron Emission Tomography / Computed Tomography (PET/CT) is a hybrid diagnostic imaging tool predominantly used in oncology cases; to diagnose and stage cancers as well as to monitor treatment response. The commonly used radio-isotope in oncology imaging is 2-(18F)-fluoro-2-deoxy-D-glucose (18F-FDG) which is a radioactive isotope tagged to a glucose analogue. Increased utility of glucose by most types of cancer cells forms the basis of PET/CT interpretation of deranged physiological uptake at a cellular level. Therefore, it is important to have a reliable quantification method to assess 18F-FDG uptake in lesions detected by this scan. There are two types of ways to quantify 18F-FDG uptake; namely visual qualitative assessment - comparing uptake in diseased tissue relative to the normal surrounding tissue, and the other is a semi-quantitative assessment using standardised uptake value. Standardised Uptake Value (SUV) is the most widely accepted method to semi-quantitatively assess lesions detected on PET/CT [1],[46],[47],[48] and [49]. This value is dependent on several factors, namely the patient's body habitus and the dose of the injected radioisotope. There is a limitation to the utility of this method, however, as this value becomes falsely increased in overweight and obese patients. This is caused by very little accumulation of FDG in white fat or adipose tissue during fasting state, hence leading to a higher FDG redistribution and uptake in non-fatty tissue [2].

Alterations in 18F-FDG intracellular metabolism is a useful non-invasive biomarker for monitoring treatment response that occurs in cancer cells. A consistent baseline reading is important to enable reliable comparison to be made in serial scans of cancer patients. Accurate measurements of relative tissue uptake of 18F-FDG are necessary. Unfortunately, these measurements are significantly influenced by variations that occur in daily clinical practice, particularly caused by the quantity of injected 18F-FDG dose and patient morphometrics [3]. Thus, we propose another semi-quantitative method of using Standard Uptake Value normalized for Lean Body Mass (SUL) which can give an improved consistency of measurements, particularly in cancer patients who have extremes of body mass index (BMI) values. As the prevalence of obesity is rising in this current decade, the utility of SUL becomes more relevant and necessary.

1.2 Problem Statement and Justification

Semi-quantitative evaluations of most 18F-FDG PET/CT scans in oncology imaging are frequently done using Standardised Uptake Value (SUV) measurements. This can be automatically calculated using a vendor installed computer-generated (CG) software. It indirectly measures the *in vivo* distribution of injected 18F-FDG in cells of body tissue. This reading is reliable in subjects who have a body weight that is within the range of the ideal body mass index (BMI). This reading, however, becomes falsely elevated in overweight and obese subjects [2],[3] and [4]. Thus, there are studies that propose using SUV normalized for lean body mass (SUL) to correct for this, especially in overweight and obese patients [5]. SUL can be acquired through computer-generated automated methods (SUL-CG), via calculations based on estimations of fat weight based on CT data [6] as well as using calculations based on predictive equations for lean body mass (LBM) such as James LBM formula and Janmahasatian LBM formula [5],[7),[38],[39] and [45]. Furthermore, as a large proportion of Malaysians currently fall in the overweight and obese category as evidenced by a recent study [8]. Thus, the issue of improving standardization of PET/CT quantitative calculations becomes even more relevant. Almost all previous studies have been based on low dose non-contrast-enhanced PET/CT scan images. Many centres nowadays perform contrast-enhanced PET/CT scans, thus there is a need to know whether the effect of contrast media would alter the standardization of SUL measurements [52],[55] and [56]. In particular obese patients may have abnormal range of readings. Hence, there is a need to identify whether SUL calculated using computer-generated values are more accurate compared to using estimates based on predictive equations for LBM staging [41].

1.3 Main Aim and Specific Objectives of the Study

The purpose of this study was to answer certain research questions.
Research questions included:

1. What is the quantitative range of measurements of SUV and computer generated SUL in the liver area?

2. What is the inter-reader agreement for measurement of
    a. SUV in non-contrast-enhanced PET/CT studies?
    b. SUL (Computer generated) in non-contrast-enhanced PET/CT studies?
    c. SUV in contrast-enhanced PET/CT studies?
    d. SUL (Computer generated) in contrast-enhanced PET/CT studies?

3. What is the correlation between the measurements of liver SUV and liver SUL (Computer-generated)
   a. In non-contrast-enhanced PET/CT scans?
   b. In contrast-enhanced PET/CT scans?
4. What are the independent variables/ factors that affect SUV and SUL measurements in contrast-enhanced PET/CT scans?

5. What is the agreement between two types of methods to measure SUL using predictive equations namely, SUL-James (PE1) and SUL-Janmahasatian (PE2)?

6. What is the correlation between SUL (using contrast-enhanced scans compared to SUL using non-contrast-enhanced scans) with
   a. BMI groups?
   b. gender ?

The overall aim of this study was to identify the agreement of SUL (computer generated) and SUL derived by predictive equations at the liver area. This study also assessed the correlation of SUL measurements in contrast-enhanced scans compared to non-contrast-enhanced scans (within different BMI groups) as a semi-quantitative parameter in 18F-FDG PET/CT oncologic imaging for Malaysian population. Subsequent research findings that arise from this study can be a source of reference for improving technique and patient management in oncology imaging in Malaysia.

Specific Objectives of this study were:

1. To identify quantitative measurements of SUV and SUL at the liver area.

2. To measure inter-reader agreement for SUV and SUL measurements.

3. To measure the correlation between the measurements of liver SUV and liver SUL (Computer-generated).

4. To find out the independent variables/ factors that affect SUV and SUL measurements in contrast-enhanced PET/CT scans.

5. To test agreement among three different methods of measuring SUL i.e. computer generated SUL (interchangeably referred to as SUL or SUL-CG), as well as predictive equations for lean body mass based on James (SUL-James) (PE1) and Janmahasatian (SUL-Janma) (PE2).

6. To measure the correlation between SUL (using contrast-enhanced scans compared to SUL using non-contrast-enhanced scans) with BMI groups and gender.

1.4 Organisation of Thesis

The organisation of this thesis is as follows. In the next chapter, we review previous works in studying the various factors that affect SUV and SUL values. We then focus on the effects of body mass index on readings of SUV and SUL. We will explain why the liver was used as a site for baseline measurements. We will then highlight the effects of extremes of BMI upon SUV and discuss the benefits of using SUL. We will also compare the reliability of various methods used for achieving SUL readings i.e. SUL computer generated and SUL derived from predictive equations. We will also discuss the significance of obesity in causing derangement of standardized baseline semi-quantitative PET/CT assessment, which will be highlighted in the last subsection in Chapter 2.

Chapter 3 provides a brief description of how we developed our study protocol. We will explain our materials and methods in conducting this study. We will discuss the need for a multicentre study and explain the statistical methods we used in analysing the study results.

In Chapter 4, we present our results from Centre A i.e. Centre for Diagnostic Nuclear Imaging, Universiti Putra Malaysia and Centre B Prince Court Medical Centre in the form of tables, graphs and PET/CT image figures. Our related work has been published in the Malaysian Journal of Medicine and Health Sciences (2017) and also presented at the International Conference of Translational Molecular Imaging and Aerospace Medicine & Physiology Showcase (2016) at KLIA, Sepang.

In Chapter 5 we highlight the discussion for the very first large scale study conducted to analyse the effects of BMI on semi-quantitative assessment of contrast-enhanced PET/CT scans. We also compare our results based on a multi-centre study involving one government-based centre that performs mainly contrast-enhanced PET/CT scans and the other a private medical centre that mainly performs plain low dose PET/CT scans. In this chapter, we also give a summary of this thesis as well as discuss significant findings from the study and directions for future works. Subsequently, there is a brief description of biographical data of the student.

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