UNIVERSITI PUTRA MALAYSIA

EFFECTS OF CONTRAST-ENHANCED POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY IN CANCER IMAGING

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By

MOHD HAFIZI MAHMUD

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

August 2015

In the Name of Allah, the Most Gracious,
the Most Merciful

This work is dedicated to my beloved parents, Mahmud Saad and Hasnah Omar and and my beloved wife as well, Nor Fatimah Ishak and my dearly sons, Abdullah Mu'az and Abdullah Wafi. Their patience, understanding, support and prayers, the complete of this work would not have been possible.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

EFFECTS OF CONTRAST-ENHANCED POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY IN CANCER IMAGING

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August 2015

Chair: ProfessorAbdul Jalil Nordin, PhD
Faculty: Medicine and Health Sciences

Integrated Positron Emission Tomography/Computed Tomography (PET/CT) with the use of fluorine-18 (^{18}F) isotope tagging with fluorodeoxyglucose (FDG) tracer (^{18}F-FDG) is becoming an important tool for clinical investigation with increase clinical utilization particularly in oncology. Application of intravenous (IV) contrast-enhanced CT (CECT) in PET imaging has been reported to lead for overestimation on the standardized uptake value (SUV) of attenuation-corrected PET. The major aim of this study was to investigate the effect of IV contrast-enhanced PET/CT scanning protocol on the CT value and PET SUV at the Centre for Diagnostic Nuclear Imaging of Universiti Putra Malaysia (CDNI UPM) in cancer imaging in view to be recommended as a standard imaging procedure.

Whole body ^{18}F-FDG PET/CT scans of 75 oncology cases performed with both non IV contrast-enhanced CT (NECT) and CECT protocols atCDNI UPM for tumour staging were reviewed. The CT value and PET FDG uptake activity as denoted by the mean Hounsfield unit (HU_{mean}) and maximum SUV (SUV_{max}), respectively of six normal tissues and lesions were quantified using a third party imaging software of OsiriX and compared between the non-contrasted and contrasted PET/CT protocols. The mean SUV_{max} of all observed lesions was determined and the SUV_{max} of liver was statistically associated with several biological and procedural related factors. The effective doses resulting from the stand-alone (NECT, CECT and PET) and integrated (summation of NECT, CECT and PET) scanning protocols were calculated by means of the published and modified dose coefficients. Statistical analysis was performed using SPSS with $p < 0.05$ considered as significant.

Statistically significant and insignificant changes were found in HU_{mean} ($p < 0.001$) and SUV_{max} values ($p > 0.05$), respectively in all normal tissues and lesions. The mean SUV_{max} of overall lesions was 9.70 ± 4.19 and 9.71 ± 4.18 for non-contrasted and contrasted lesions, respectively. The SUV_{max} of the liver was significantly influenced by age, body mass index (BMI), fasting blood glucose level and incubation period ($p < 0.05$) as shown by multiple linear regression analysis. The mean effective doses contributing from CT and PET were 21.13 ± 4.62 mSv and 5.75 ± 0.50 mSv, respectively, resulting in the total whole body PET/CT effective dose of 26.89 ± 4.75

mSv. A statistically significant difference of effective doses was found among the three stand-alone scanning protocols ($p < 0.001$).

As a conclusion, this study revealed no significant changes in the semiquantification uptake value of attenuation corrected PET as a result of utilization of the IV CECT protocol in PET/CT imaging. The highly cut-off value of SUV_{max} (9.70 – 9.71) of cancerous lesions was acquired in the CDNI UPM. Age, BMI, fasting blood glucose level and incubation period were significant factors influencing the physiological FDG uptake of the liver. The mean total patient effective radiation dose resulting from the total whole body PET/CT study was 26.89 ± 4.75 mSv. Therefore, contrasted contemporaneous PET/CT protocol canbe usedas a first line tool in routine PET/CT study in selectedoncologycases optimizing the value of this integrated imaging modality for clinical investigation of cancer disease.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Sarjana Sains

KESAN TOMOGRAFI PANCARAN POSITRON/TOMOGRAFI BERKOMPUTER BERPENCERAHAN KONTRAS DALAM PENGIMEJAN KANSER

Oleh

MOHD HAFIZI BIN MAHMUD

Ogos 2015

Pengerusi: Professor Abdul Jalil Nordin, PhD
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Integrasi Tomografi Pancaran Positron/Tomografi Berkomputer (PET/CT) dengan penggunaan *fluorine-18* (^{18}F) isotop yang dilabelkan bersama radiofarmaseutikal *fluorodeoxyglucose* (FDG) (^{18}F-FDG) merupakan sebuah alat yang penting untuk kajian klinikal dengan peningkatan aplikasi klinikal terutamanya dalam bidang onkologi. Penggunaan CT dengan intravena (IV) berpencerahan kontras (CECT) dalam pengimejan PET telah dilapor menyebabkan anggaran yang tinggi terhadap nilai pengambilan standard (SUV) dari *attenuation-corrected PET*. Tujuan utama kajian ini adalah untuk menyiasat kesan protokol pengimbasanPET/CT berkontras intravena ke atas nilai CT and SUV PET di Pusat Pengimejan Diagnostik Nuklear Universiti Putra Malaysia (PPDN UPM) dalam pengimejan kanser yang disyorkan sebagai sebuah prosedur pengimejan standard.

Imbasan seluruh badan ^{18}F - FDG PET/CT yang melibatkan 75 kes onkologi yang telah dijalankan dengan kedua-dua protokol CT tanpa pencerahan kontras IV (NECT) dan CT dengan pencerahan kontras IV (CECT) di PPDN UPM untuk penilaian tahap kanser telah dikaji. Nilai CT danpengambilan aktiviti FDG PET seperti ditunjukkan masing-masing oleh nilai purata unit Hounsfield(HU_{mean}) dan nilai maksimum SUV (SUV_{max}) terhadap enam tisu normal dan tisu tumor telah dikira menggunakan perisian pengimejan pihak ketiga OsiriX dan dibandingkan antara protokol PET/CT yang berkontras dan tidak berkontras. Nilai purata SUV_{max} tisu tumor juga telah ditentukan dan SUV_{max} hati telah dihubungkaitkan secara statistik dengan beberapa faktor biologi dan faktor prosedur yang berkaitan. Dos efektif yang diperolehi daripada imbasan individu (NECT, CECT dan PET) dan imbasan integrasi (penjumlahan kepada NECT, CECT dan PET) telah dikira dengan menggunakan pekali dos yang telah dilaporkan dalam penerbitan dan juga yang telah diubahsuai. Analisa statistik dilakukan dengan menggunakan perisian SPSS dengan $p < 0.05$ dianggap sebagai nilai signifikan.

Perubahan yang signifikan dan tidak signifikan secara statistik masing-masing telah ditemui dalam nilai HU_{mean} ($p < 0.001$) dan SUV_{max} ($p > 0.05$) dalam semua tisu normal dan tisu tumor. Purata SUV_{max} secara keseluruhan untuk tisu tumor adalah masing-masing 9.70 ± 4.19 dan 9.71 ± 4.18 untuk tisu tumor tidak berkontras dan berkontras. Umur, indeks jisim badan, tahap glukosa darah puasa dan tempoh inkubasi didapati

berhubungkait secara signifikan dengan SUV_{max} hati ($p < 0.05$) sepertimana ditunjukkan oleh analisis regresi linearberganda. Min dos berkesan yang diperolehi dari CT dan PET adalah masing-masing 21.13 ± 4.62 mSv and 5.75 ± 0.50 mSv yang menghasilkan jumlah dos berkesan PET/CT seluruh badan sebanyak 26.89 ± 4.75 mSv. Perbezaan yang signifikan secara statistik telah didapati antara ketiga-tiga protokol pengimbasan individu ($p < 0.001$).

Kesimpulannya, kajian ini mendedahkan bahawa tiada perubahan dan anggaran tinggi yang signifikan daripada nilai pengambilan semikuantifikasi *attenuation correctedPET* kesan daripada penggunaan protokol *IV CECT* dalam pengimejan PET/CT. Nilai purata SUV_{max} yang tinggi (9.70 – 9.71) untuk tisu tumor diperolehi di PPDN UPM. Umur, indeks jisim badan, tahap glukosa darah puasa dan tempoh inkubasi adalah faktor signifikan yang mempengaruhi fisiologi pengambilan FDG untuk hati. Min jumlah dos radiasi berkesan pesakit hasil dari pemeriksaan PET/CT seluruh badan adalah sebanyak26.89 ± 4.75 mSv. Oleh itu, protokol PET/CT berpencerahan kontras boleh digunakan sebagai protokol awal dalam pemeriksaan rutin PET/CT dalam kes-kes onkologi terpilih dengan mengoptimumkan nilai modaliti bersepadu ini untuk siasatan klinikal bagi penyakit kanser.

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To all of them, may Allah reward and bless their sincerity, kindness and dedication.

Thank you.

I certify that a Thesis Examination Committee has met on 17 August 2015 to conduct the final examination of Mohd Hafizi bin Mahmud on his thesis entitled "Effects of Contrast-Enhanced Positron Emission Tomography/Computed Tomography in Cancer 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 rewarded the Master of Science.

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LIST OF ABRREVIATIONS

2-D	Two-dimensional
3-D	Three-dimensional
AEC	Automatic Exposure Control
AJCC	American Joint Committee on Cancer
ANOVA	Analysis of variance
ATP	Adenosine triphosphate
BaF_2	Barium fluoride
BGO	Bismuth germinate
BMI	Body mass index
CDNI	Centre for Diagnostic Nuclear Imaging
CECT	Contrast-enhanced CT
CEPET	Contrast-enhanced PET
CI	Confidence interval
CT	Computed Tomography
CTDI	Computed Tomography Dose Index
$CTDI_{vol}$	Volume Computed Tomography Dose Index
$CTDI_w$	Weighted Computed Tomography Dose Index
DICOM	Digital Imaging and Communications on Medicine
DLP	Dose Length Product
DSCT	Dual-source CT
FBG	Fasting blood glucose
FDA	Food and Drug Association
FDG	Fluorodeoxyglucose
FOV	Field of view
FWHM	Full width at half maximum
GLUTs	Glucose transporters
GSO	Gadolinium oxyorthosilicate doped with cerium
HD PET	High Definition PET
HU	Hounsfield unit
HU_{mean}	Mean Hounsfield unit
IARC	International Agency for Research on Cancer
ICRP	International Commission of Radiological Protection
IIUM	International Islamic University Malaysia
IL-6	Interleukins-6
IUCC	International Union for Cancer Control
IQR	Interquartile range
JAKIM	Department of Islamic Development Malaysia
keV	kilo electron volt
LOR	Line of response
LSO	Lutetium oxyorthosilicate doped with cerium
MBq	Mega Becquerel
mCi	Millicurie
mCT	Molecular CT
MDCT	Multidetector CT
MeV	Mega electronvolt

mGy	Milli gray
MIP	Maximum Intensity Projection
mmol/L	millimol per litre
MRI	Magnetic Resonance Imaging
NaI(Tl)	Sodium iodide doped with thalium
NECT	Non contrast-enhanced CT
NEPET	Non contrast-enhanced PET
PACS	Picture Archiving and Communication System
PET	Positron Emission Tomography
PET/CT	Positron Emission Tomography/Computed Tomography
PET/MRI	Positron Emission Tomography/Magnetic Resonance Imaging
PET/NECT	Positron Emission Tomography/ Non contrast-Enhanced CT
PET/CECT	Positron Emission Tomography/Contrast-Enhanced CT
PMT	Photomultiplier tube
ROC	Receiver operating characteristic
ROI	Region of interest
RUGS	Research University Grant Scheme
SD	Standard deviation
SNR	Signal noise ratio
SPECT	Single Photon EmissionTomography
SPECT/CT	Single Photon Emission Tomography/ Computed Tomography
SPSS	Statistical Package for Social Sciences
SUV	Standardised uptake value
SUV_{lbm}	SUV normalized for lean body mass
SUV_{max}	Maximum standardised uptake value
SUV_{weight}	SUV normalized for body weight
Tc-99m	Technitium-99m
TLD	Thermoluminescent dosimeter
TNM	Tumour node metastasis
TNF-α	Tumour necrosis factor alpha
TOF	Time of flight
UiTM	Universiti Teknologi MARA
UPM	Universiti Putra Malaysia
WHO	World Health Organisation
YSO	Yttrium oxyorthosilicate doped with cerium

LIST OF NOTATIONS

A	Administered radioactivity of FDG
b	Adjusted standardised beta coefficient
D	Thickness of medium
D_T	Absorbed radiation dose in organ or tissue
$D(z)$	Dose distribution along a line parallel to the z-axis
E	Effective dose
H_e	Effective dose equivalent
H_T	Tissue dose equivalent
Γ_E^{FDG}	Absorbed dose coefficient value of organ or tissue for FDG
Γ_r^{FDG}	Effective dose coefficient value for FDG
mA	Tube current
OH	Hydroxyl
p	Density
T	Nominal slice thickness
μ	Linear attenuation coefficient
μ/ρ	Mass attenuation coefficient
W_T	Tissue weighting factor
ΣWT	Summation of tissue weighting factor
Z_{eff}	Effective atomic number

CHAPTER 1

INTRODUCTION

1.1 Background

Whole body scanning of integrated Positron Emission Tomography/Computed Tomography (PET/CT) with the use of fluorine-18 (^{18}F) isotope tagging with fluorodeoxyglucose (FDG) tracer (^{18}F-FDG) has been established today as a major tool in diagnosis and staging of a wide variety of cancers. ^{18}F-FDG Positron Emission Tomography (PET) has been considered as a valuable imaging modality to provide qualitative and quantitative metabolic information of a tumour (Blake, Singh, Setty, Slattery, Kalra, Maher, Sahani, Fischman and Mueller, 2006). A comprehensive review of the ^{18}F-FDG PET oncology literature has reported the superior performance of this imaging modality in the diagnosis, staging, detection of recurrence, restaging and monitoring of therapy for most malignant tumours (Gambhir, Czernin, Schwimmer, Silverman, Coleman and Phelps, 2001). Before the integrated imaging modality was discovered, ^{18}F-FDG PET images suffer from poor resolution, especially in detecting small size lesion. To improve the image quality, PET images are modified by attenuation correction using gamma ray sources such as germanium 68 (Blodgett, Meltzer and Townsend, 2007). However, the disadvantage of this technique is time consuming. Integration of morphological and functional information in a single modality of PET/CT leads to the enormous development in the detection and evaluation of lesion (Nordin,AJ, Abdul Rahim, N, Ahmad Saad, FF and Azman, AZF, 2012).

CT is a well-known diagnostic radiological imaging modality which is a useful tool in cancer staging, localizing infection and inflammatory lesions and evaluation of treatment response. Capability of CT in precise anatomical delineation helps surgical decision and accurate staging. Non-contrast enhanced CT (NECT) and low dose CT has been acceptable in major PET/CT practice as it offers cost effective and less radiation exposure to patients. However, contrast-enhanced CT (CECT) or known as diagnostic CT is preferred over NECT for cancer staging. Contrast administration is required to improve delineation and localization of lesions (Cronin, Prakash and Blake, 2010) and exclude local invasion of lesions (Nordin, AJ et al, 2012). Additionally, lesion characterization can be acquired through multiphase CT study in cancer diagnosis. When CT was integrated into PET, the strength of both modalities is combined together whereby the CT is used purposely for attenuation correction of PET data (Bailey, Karp and Surti, 2005). In fact, there are varieties of integrated PET/CT imaging protocols performed in different centres such as low dose CT and PET, NECT/PET, both contemporaneous NECT/PET and CECT/PET and CECT acquisition separately with PET acquisition.

1.2 Problem statement

The main concern over contrast-enhanced PET/CT protocol is an overestimation of standardized uptake value (SUV) as a consequence of the variance in the attenuation properties of the contrast media when CT is integrated with PET(Mawlawi, Erasmus, Munden, Pan, Knight, Macapinlac, Podoloff and Chasen, 2006). This overestimation characterised by contrast-induced artifacts in attenuation corrected PET images

(Antoch, Veit, Bockisch and Kuchl, 2011). This work addresses the question whether contrast-enhanced PET/CT protocol could influence the SUV of PET in cancer patients at the Centre for Diagnostic Nuclear Imaging of Universiti Putra Malaysia (CDNI UPM).

One of the prominent advantages of functional imaging using PET technology is the ability to semiquantify the FDG uptake which corresponds to the tissue metabolic activity. The quantification process is performed using a unitless formula called SUV. SUV cut-off value of 2.5 demarcating between benign and malignant tumours has been debated in the literatures. However, this cut-off value is limited due to a varied tumour histological characteristic in malignant tumour (Taylor, Smith, Brix, Wick, Theodosakis, Swenson, Kozowere, Lau and Jones, 2009). Hence, this study will explore a suitable cut-off value to be utilized at the CDNI UPM in identifying non-malignant and malignant lesions using a standard protocol for patient preparation and imaging sequences.

High FDG uptake is not only expressed in malignant tissue alone (Lin, Ding, Liu, Chen, Lin, and Kao, 2007). It is essential to know the varying degree of FDG uptake in normal tissues. Physiological FDG uptake in normal liver is utilized as the reference standard for diagnosis (Perri, Erba, Volterrani, Guidocco, Lazzeri, Caramell and Mariani, 2011; Ozcan Kara, Kara, Kara Gedik, Kara, Sahin, Ceylan Gunay and Sari, 2011), quality control (Bayani, Selvarajah, Maire, Vukovic, Al-Romaihd, Zielenska and Squire, 2007) , therapy assessment (Yon, Kyung, Byung-Tae, Joon, Young and Chin, 2006)and prognosis(Shiono, Abiko, Okazaki, Chiba, Yabuki and Sato, 2011) in PET/CT imaging. The dependent factors originating from biological influences and procedure-related factors including age, body mass index (BMI), incubation period, fasting blood glucose level and FDG administration dose on FDG uptake of normal liver will be investigated.

The increased demand for PET/CT study in oncology diagnosis and management and other clinical indications has led to increase the awareness and concern of radiation exposure of PET/CT among the clinical personnel and patients. FDG PET/CT patient radiation doses have been reported extensively in the literatures with various imaging protocols. In fact, there are insufficient evidence-based reports describing the radiation exposure resulting from FDG PET/CT study in the local population. Yet, it would be valuable to investigate the radiation dose of patients who undergoing FDG PET/CT examinationfor cancer imaging in the local population with employment of a standard imaging protocol in the present study.

1.3 Significance of the study

The clinical practice of integrated PET/CT imaging varies greatly between institutions. The current clinical method of tumour respond assessment is being revised. There is a worldwide concerned over high variations in PET/CT results between institutions using different equipment and acquisition protocol. Hence, this study is identified to be significantly important to support the extensive evidences on the value of intravenous (IV) CECT in PET/CT imaging. This study will highlight some novelties on the CECT protocol using the current settings and protocols of PET/CT study, including utilization of 64-slices multidetector CT (MDCT) and lutetium oxyorthosilicate (LSO) crystal

detector of PET and employment of automatic pressure injector for contrast administration.

The metabolic activities of the FDG-avid lesions as depicted by maximum semiquantitative uptake values (SUV_{max}) could indicate the aggressiveness of the lesion. The cut-off value of SUV_{max} of varied cell lines tumour in this study might be used to revise the traditional cut-off value of 2.5 SUV_{max} differentiating between benign and malignant tumour. Thus, this study will highlight the value of ^{18}F-FDG PET/CT as a potential molecular marker in assessing the degree of tumour aggressiveness.

It is vital to concern on various factors which could influence the physiological FDG uptake of the liver in PET/CT study to avoid misinterpretation of false positive uptake. Therefore, investigation of potential biological and procedural related factors leads to understand the significance factors influencing the FDG uptake of liver. As a consequence, special considerations should be taken into account of those significant factors ensuring accurate interpretation for accurate clinical management of a patient in PET/CT study.

The findings of effective dose are vital concerning patient radiation dose resulting from whole body FDG PET/CT examination. These findings will be compared with the previously reported FDG PET/CT doses. Furthermore, thesefindings would lead for justification and optimization of PET/CT protocols.

1.4 Hypotheses

The purpose of the study is to test the following hypotheses:

Hypothesis 1
The application of IV contrast-enhanced CT in FDG PET/CT imaging does not cause significant changes on the SUV of attenuation corrected PET images.

Hypothesis 2
The lesions presented in this study exhibit a high intensity of FDG uptake.

Hypothesis 3
Age, BMI, fasting blood glucose level and incubation period are significant factors influencing the physiological FDG uptake of the liver.

Hypothesis 4
The effective radiation dose of patients who has undergone whole body PET/CT scanning is expected lower than the previously reported values in the journal articles.

1.5 Aims of the study

The study is dedicated to addressing the current issue of ^{18}F-FDG PET/CT imaging study. The primaryaim of this study is to investigate the contrast enhanced PET/CT imaging protocol at the CDNI UPM in cancer imaging in view to be recommended as a standard imaging procedure.

Thus, the specific objectives are:

1. To study the effect of IV contrast-enhanced CT on CT value and PET SUV.
2. To determine the appropriate cut-off value for SUV_{max} of various cancerous lesions using a standard protocol for PET/CT imaging at the CDNI UPM.
3. To identify the non-modifiable biological and procedural related factors that can influence the physiological FDG uptake of the liver.
4. To estimate the patient effective radiation dose contributing from the whole body PET/CT scanning protocol at the CDNI UPM.

1.6 Thesis outline

The descriptions of the remaining chapters of this thesis are explained briefly as follows:

- Chapter 2 addresses a reviewof the operating principle of PET, CT and integrated PET/CT scanning and briefly describes about ^{18}F-FDG.Radiation aspects of PET/CT imaging and a brief overview of cancer are addressed as well in this chapter.
- Chapter 3 describes the details on whole body ^{18}F-FDG PET/CT protocols that have been used in the study. This chapter describes on quantification of the amount of changes in the Hounsfield unit (HU) of CT and SUV of PET in the selected tissues and lesions caused by the utilization of iodine-based IV contrast-enhanced CT in PET/CT imaging. Descriptive and inferential analyses on SUV_{max} of investigating lesions and several factors affecting physiological FDG uptake of liver are mentioned as well. This chapter also presents the calculation of PET/CT effective dose in stand-alone and integrated scanning protocols.
- Chapter 4 describes the results of the above mentioned studies.
- Chapter 5 discusses the findings and justifications behind the results of this study.
- Chapter 6 summarizes all the findings and states the conclusions of this research work. Some limitations of the study, recommendations and future research are outlined as well in this chapter.

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