RADIATION DOSIMETRY OF PATIENTS UNDERGOING ^{18}F-FDG PET-CT: A RETROSPECTIVE STUDY

DHALISA BINTI HUSSIN

UNIVERSITI SAINS MALAYSIA

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by

DHALISA BINTI HUSSIN

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LIST OF ABBREVIATIONS

ALARA	As Low As Reasonably Achievable
AEC	Automatic Exposure Control
ALI	Annual Limit of Intake
ARS	Acute Radiation Syndroms
B.F	Branching Factor
BMI	Body Mass Index
BSS	Basic Safety Standard
C.F	Calibration Factor
CT	Computed Tomography
CTC	Coincidence Time Correction
CTDI	CT Dose Index
CRS	Chronic Radiation Syndroms
DF	Dose Factor
DLP	Dose Length Product
EPD	Electronic Pocket Dosimeter
FBP	Filtered Back Projection
FWHM	Full Width Half Maximum
^{18}F-FDG	2-[18F] Fluoro-2-deoxy-D-Glucose
IAEA	International Atomic Energy Agency
ICRP	International Commission on Radiological Protection
ICRU	International Commission on Radiation Units
IKN	Institut Kanser Negara
IV	Intravenous
LET	Linear Energy Transfer

LOR	Line of Response
LSM	Least Squares Method
MCP	Maximum Concentration Permissible
MIRD	Medical Internal Radiation Dose
MIRDOSE	Medical Internal Radiation Dose
MIP	Medical Interface Programme
NMRR	National Medical Research Registration
NURBS	Non-Uniform Rational B-Spline
OLINDA/EXM	Organ Level INternal Dosimetry Assessment / EXponential Modelling
OSEM	Ordered Subset Expectation Maximisation
OSL	Optically Stimulated Luminescence
PET	Positron Emission Tomography
PET-CT	Positron Emission Tomography-Computed Tomography
PMOD	Periphery Module Software
QA	Quality Assessment
QC	Quality Control
RADAR	Radiation Dose Assessment Resource
ROI	Region Of Interest
SAF	Specific Absorbed Fraction
SIMDOSE	SIMulation DOSE
SPSS	Statistical Package Social Science
TAC	Time Activity Curve
TLD	Thermoluminescent Dosimeter
VOI	Volume Of Interest

LIST OF SYMBOLS

Ã	Cumulated Activity
Φ	Specific Absorbed Fraction
ϕ	Absorbed Fraction
U_s	Uptake activity in the source
τ	Residence Time
$U(t)$	Area under Uptake Curve on target
$A(t)$	Activity at time, t
H	Absorbed dose
E	Effective dose
A_0	Administered activity
S-value	Fraction of energy released per nuclear decay in a source volume reaching a target region, normalised to target region mass (mGy/MBq-h)
T_e	Effective half-life
f_h	Fraction of A_0 deposited into organ of concern

DOSIMETRI SINARAN TERHADAP PESAKIT YANG MENJALANI PEMERIKSAAN ^{18}F-FDG PET-CT : SATU KAJIAN RETROSPEKTIF

ABSTRAK

Pesakit ^{18}F-FDG PET-CT menerima dedahan radiasi daripada radiofarmaseutikal dan komponen CT. Objektif kajian ini adalah membuat penilaian dos sinaran pesakit dengan menggunakan kaedah pengiraan matematik dan pengukuran secara eksternal. Seramai 234 orang dewasa menjalani imbasan PET-CT tunggal dan 83 orang daripadanya telah menjalani imbasan tambahan PET-CT pada hari yang sama. 25 pesakit kanak-kanak menjalani imbasan tunggal PET-CT. Penilaian dos organ adalah menggunakan aplikasi PMOD dan OLINDA/EXM untuk organ jantung, hati, buah pinggang dan pundi kencing. Keputusan masa diam organ hati adalah lebih lama diikuti organ lain seperti buah pinggang, pundi kencing dan jantung dengan masing-masing 0.593 j ± 0.055 j, 0.434 j ± 0.031 j, 0.361 j ± 0.061 j and 0.326 j ± 0.024 j. Nilai purata dos organ terserap adalah 0.028 mGy, 0.045 mGy, 0.084 mGy and 0.006 mGy bagi jantung, buah pinggang, hati dan pundi kencing. Penilaian dos efektif seluruh tubuh adalah berdasarkan garis panduan ICRP. Dos efektif seluruh tubuh untuk pesakit dewasa yang menjalani imbasan tunggal dan imbasan tambahan adalah 16.69 mSv ± 4.01 mSv dan 23.25 mSv ± 2.67 mSv. Dos efektif seluruh tubuh untuk pesakit kanak-kanak yang menjalani imbasan tunggal PET-CT adalah dalam julat 8.24 mSv ± 2.01 mSv to 14.23 mSv ± 2.67 mSv (dari peringkat umur 0 sehingga 16 tahun). Keputusan pengukuran dos sinaran secara eksternal menggunakan meter tinjau pada jarak 1 meter dan pada permukaan seluruh tubuh adalah masing-masing 106.09 μSvj^{-1} ± 40.33 μSvj^{-1} and 7.55 μSvj^{-1} ± 1.05 μSvj^{-1}. Anggaran jumlah kumuhan (urin) adalah 31.47 MBq ± 19.89 MBq dalam tempoh masa 185.25 min ± 30.32 min sepanjang berada di premis PET-CT ini. Didapati keputusan dos organ terserap dan dos

efektif seluruh tubuh adalah relevan kerana pesakit adalah penghidap kanser. Dedahan dos radiasi pesakit yang dibenarkan pulang ke rumah adalah selamat kepada orang awam.

RADIATION DOSIMETRY OF PATIENTS UNDERGOING ^{18}F-FDG PET-CT : A RETROSPECTIVE STUDY

ABSTRACT

^{18}F-FDG PET-CT patients are exposed to radiation doses from radiopharmaceuticals and the CT component respectively. The objective of this study was to perform the patient dose assessment based on calculations and measurements. The collected data were of 234 adults who underwent single PET-CT exams while 83 were those who underwent another sequential PET-CT examination on the same day of appointment at Institut Kanser Negara (IKN). 25 paediatrics underwent a single PET-CT examination. Organ dose assessment was performed using the PMOD and OLINDA/EXM software for heart, liver, kidney and urinary bladder. For adults the mean residence time result for liver is the longest, followed by kidney, urinary bladder and heart with mean average of 0.593 h ± 0.055 h, 0.434 h ± 0.031h, 0.361 h ± 0.061h and 0.326 h ± 0.024 h respectively. The mean result for organ absorbed dose of adult was 0.028 mGy, 0.045 mGy, 0.084 mGy and 0.006 mGy for heart, kidney, liver and bladder respectively. The whole-body PET-CT effective dose was determined from ICRP guidelines and the result of single and sequential PET-CT examination for adult was 16.69 mSv ± 4.01 mSv and 23.25 mSv ± 2.67 mSv respectively, while, paediatric patient ranged from 8.24 mSv ± 2.01 mSv to 14.23 mSv ± 2.67 mSv within the age from 0 to 16 years old. The patient mean dose rate reading at the surface and at 1 m before being discharged was 106.09 $\mu Svhr^{-1}$ ± 40.33 $\mu Svhr^{-1}$ and 7.55 $\mu Svhr^{-1}$ ± 1.05 $\mu Svhr^{-1}$ respectively. The estimation of mean urine excretion was 31.47 MBq ± 19.89 MBq within 185.25 min ± 30.32 min of spent time in this Centre. The result of this study for organ absorbed and whole-body PET-CT effective dose is relevant as the

selection of patient was suspected with metastasis disease and the patient discharged level from this Centre is safe for public.

CHAPTER 1

INTRODUCTION

1.1 Background

Positron Emission Tomography Computed Tomography (PET-CT) is a hybrid technology with a great combination of PET and CT scanners that gives metabolic or molecular information and cross-sectional information on anatomy respectively. PET-CT has the ability to differentiate between benign or malignant tissue by localising the response of increased uptake of 2-[18F]Fluoro-2-deoxy-D-Glucose (^{18}F-FDG) activity (Basu et al., 2011). With this such great capability in tumour determination, the system is more sensitive in quantitative and qualitative imaging that becomes a great choice to develop a rational treatment planning to the patient and guide the clinician to decide for further therapy by either conforming response or signaling the need for a change in therapy (Boellaard, 2011).

PET-CT scanner is widely used in diagnostic, staging and re-staging, monitoring response to therapy and detection of various types of early malignancies (Almuhaideb et al., 2011). It has been recognised to confirm the presence of tumour in the early stages (Boellaard et al., 2015).

Recently, there is a demand in using PET-CT with ^{18}F-FDG in the clinical multidisciplinary field of nuclear medicine (Farwell et al., 2014). The awareness in dose minimisation demanding due to expanding record of patient listing which keep increasing. This Centre reported that the number of PET-CT examinations increased by more than100 cases per year which is over 500 cases in 5 years since 2010 to 2015. There was an increment of 20% paediatric cases since 2010 to 2015 (Kementerian Kesihatan Malaysia, 2016).

PET-CT imaging is also referred to as molecular imaging. It uses radiopharmaceuticals such as ^{18}F-FDG as a tracer in the field of nuclear medicine and is well established in imaging technique. The main role of the tracers is to identify the interaction of chemical and biological system that responded to molecular changes. In other words, radionuclides in diagnostic imaging and research purpose are widely use because of the advantage of bio-distribution information from the radiopharmaceutical.

Patients who undergo PET-CT examination receive internal and external radiation dose exposures (Leide-Svegborn, 2010) originating from the administered radioactivity and CT component respectively. Generally in PET-CT, the radioactive tracer contributed more radiation dose to the patient rather than CT (Brix et al., 2005). This is because CT in PET-CT imaging uses the low dose CT compared to general CT which is specifically for diagnostic examinations (Zaidi, 2007). CT-based attenuation correction functions in PET-CT is able to reduce the emission imaging scan which these benefits most to the dose reduction with the aim to balance the examination benefits with the risk from radiation exposure. This cannot be obtained with a single scan of CT or PET alone (Cherry, 2009).

There is no dose limit to the patient in diagnostic and therapeutic procedures, but the urge of optimisation and radiation risk effect must balance the need. The possibility of having late radiation effects such as cancer became higher.

Due to this concern, the International Atomic Energy Agency (IAEA) has provided guidelines to apply the radiation safety standards in nuclear medicine for protection against ionising radiation (Strzelczyk, 2006) which also comply with the Basic Safety Standard (BSS) needs. BSS (Strzelczyk, 2006) stated that the principle, justification, and optimisation of protection requirements in nuclear medicine or medical line are applied to medical exposure but not the dose limitation. In diagnostic medical exposure, the radiation dose level needs to be kept at a minimum level as the required diagnostic objective is achieved. To achieve this requirement, the radiation dose assessment to the patient is required to estimate the radiation dose to the whole-body as well as the critical organ.

In clinical procedures, patient radiation dosimetry is important. Patients receiving radiopharmaceuticals via ingestion or injection are exposed to internal exposure. Definition of radiation dosimetry is dose assessment from the ionising radiation usage. The suggested estimation value to represent the amount of radiation exposure is, absorbed dose or effective dose. The absorbed dose is very important to determine how much radiation dose is received in the specific organ, while the effective dose is powerful in radiological protection for estimating the stochastic risk effect. The dose assessment can be done by performing calculations and external measurements. Calculations are nowadays simplified in softwares that apply the mathematical principles. While external measurements refer to the use of dosimeter or radiation

instrumentation. Patient specific dosimetry refers to individually and organ specific calculations. Every patient has different of biokinetic assessment, therefore the need of delivered correct radiation amount to the patient in diagnostic area estimate the potential radiation risk effects to the patient.

Potential of patient benefit-risk due to the radiation exposure in both clinical and research application must be justified compared to associated risk (Strzelczyk, 2006). The potential radiation risk to the patient is non-stochastic (tissue reaction) and stochastic effect. The radiation risk of most concern is that due to the tissue reaction effect. Tissue reaction effect can be erythema, epilation, depression of bone marrow cell division, nausea, vomiting, diarrhea, central nervous system damage, fetal damage or death (Stabin (a)., 2008). Stochastic effect refers to the probability of having certain effects such as cancer and genetic effects. These are considered as late effects where, it may occur years or decades after the exposure.

The basic fundamental in radiation dosimetry is based on the important information such as cumulative dose and residence time where these results led to organ absorbed dose in Gray units, however, other factor like organ weight also affect S-value in dosimetry. Besides that, the kinetic selection in dosimetry which gave the result of organ residence time which these also contribute the existence of ambiguity in the dose result as well.

Guidelines in radiation dosimetry are provided by special task groups formed internationally like the International Commission on Radiological Protection (ICRP), the Medical Internal Radiation Dose (MIRD) committee and the Radiation Dose

Assessment Resource (RADAR) as they are concerned with radiation workers and patient dose exposure. They gathered all the information as for example in MIRD edition, they provided a radiation dosimetry handbook written from the beginning of data collection until the analysis of the results of patients that underwent nuclear medicine examinations. The progress in radiation dosimetry improved tremendously over the years. This task group invented mathematical modelling software such as Simulation De Dose (SIMDOSE), Medical Internal Radiation Dose (MIRDOSE) and Organ Level Internal Dosimetry Assessment/ Exponential Modelling (OLINDA/EXM) for patient dose calculation. This has been accepted worldwide (Stabin et al., 2012).

The softwares are equipped with geometrical phantoms with different age, gender, and gestation period similar to the normal human anatomy. The phantoms were designed based on robust data collected under the IAEA internal dosimetry project. This tool was helpful and proven clinically reliable to the physicists and physicians (Stabin et al., 2005). Moreover, the upgraded version of the software has a flexible option to manipulate the organ weight to get dose results that mimic real patients and this is no doubt to be most suitable for specific patient dosimetry.

1.2 Problem Statement

From the literature review, the obtained result of whole-body PET-CT effective dose for adult and paediatric patients in this Centre was among the highest (Khamwan et al., 2010). This is based on a study done by Abdullah et al. (2014) and Hussin et al., (2016) where during their data collection, the PET-CT scanner was not equipped with

Automatic Exposure Control (AEC) function and both studies were done at Hospital Putrajaya and Institut Kanser Negara respectively.

Patients who underwent ^{18}F-FDG PET-CT were exposed to high radiation doses in this Centre due to the following reasons :

1) Peadiatric patients were scanned using the whole-body adult protocol and they were exposed to high CT doses.
2) Patients underwent another sequential PET-CT examination on the same day of appointment, which again means patients were exposed to unnecessary external exposure.
3) Determination of patient doses was difficult due to the unique biokinetics. In previous practice, patient dose estimation was based on a reference source (dose calculation was based from average population), but, in this study patient specific dosimetry approach was used. This is important since specialists prescribe and give the exact dose to cure the illness and at the same time minimise the radiation health effects. This is in line with many studies done on patient dosimetry (Kolbert et al., 1997; Tsougos et al., 2010; Mattsson, 2015).
4) In previous studies, the PET-CT scanner was not equipped with the AEC function. This PET-CT scanner was in operation until April, 2015. The AEC function is a dosimetry tool and it is used to optimise radiation exposure based on tissue density while maintaining the image quality.

Later in May 2015, the PET-CT scanner in this Centre was installed with Automatic Exposure Control (AEC) function. Therefore, a comparison on dose reduction effectiveness with the use of AEC function was evaluated based on data collection before and after installation.

1.3 Objective of Study

The main objective of this study was to evaluate radiation dose received by the patients underwent ^{18}F-Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography (PET-CT) examinations in nuclear medicine department, Institut Kanser Negara (IKN), Putrajaya by performing radiation dosimetry by calculations and by measurements.

The specific objectives are as follows:

A. Dosimetry by calculation :

a) to estimate the organ absorbed dose from obtained results of residence time of the selected organs and patients using OLINDA/EXM software.

b) to calculate the whole-body PET-CT effective dose of the adult and paediatric patients based on ICRP guidelines.

B. Dosimetry by measurement :

a) to collect the radiation dose exposure of patients underwent ^{18}F-FDG using calibrated survey meter before discharged from this Centre at 1 metre distance and at surface of trunk area.

1.4 Scope of Study

This is a retrospective study that covers patient specific dosimetry and radiation risk estimation based on the results of internal and external dosimetry. This study focused on assessment of organ absorbed dose, whole-body effective dose and dose rate exposure of the patient. The organ absorbed dose was estimated using OLINDA/EXM

software while whole-body PET-CT effective dose determination was performed as recommended by ICRP.

The selection of patients was done by nuclear medicine specialists and physicists at IKN centre. 80% was covered in patient dosimetry, while another 20% in PET-CT imaging. This retrospective study was under ethics approval obtained from Ministry Of Health (MOH-NMRR) and Jawatankuasa Etika Penyelidikan (Manusia) of USM (JEPeM).

The tools for imaging and dosimetry calculation such as PMOD and OLINDA/EXM software was used in this study. No biological sample involved in this work. The dosimetry calculation was performed on data retrieved with the permission from nuclear medicine department, IKN. There was no physical contact with patients and no volunteer participant was involved in this study.

1.5 Thesis organisation

This thesis consists of five chapters.

Chapter 1 presents an introduction to the thesis. It also discusses the importance of radiation dosimetry assessment in clinical applications because of the high demand of diagnostic nuclear medicine. The importance of having patient dose evaluation is to acknowledge the radiation risk associated with these procedures. This Chapter also presents the problem statement, objectives and scope of the study.

Chapter 2 discusses the history and development of nuclear medicine dosimetry. The function of radionuclide and radiopharmaceuticals as tracer in nuclear medicine is important in order to obtain good images on the behaviour of the disease. In radiation dosimetry, the description of phantom, method of calculation and uncertainties is explained in this Chapter. The radiological risk issue such as biological effects which refer to deterministic or stochastic effects are also included whereby the evaluation of the patient risk-benefit is an important consideration in nuclear medicine dosimetry.

Chapter 3 discusses materials and methodology involved in this study. The data collection is explained in this Chapter. The dosimetry calculation and the use of suitable statistic such as SPSS in data analysis is also presented. The use of mathematical softwares Periphery MODule (PMOD) and Organ INternal Dose Assessment/ EXponential Modelling (OLINDA/EXM) as an internal dosimetry tool in this study and the statistical analysis is also discussed in this Chapter.

Chapter 4 presents results and discussions of this study. The main result of this study is divided into two (2) sections where part one (1) covers dosimetry by calculation which focused on absorbed dose and whole-body PET-CT effective dose while part two (2) covers dosimetry by measurement which referred to external measurement using the OSL and survey meter. The radiation dosimetry was based from ICRP and RADAR perspective. The obtained result also attached with dedicated graphs and tables to ensure well explanation in the discussion section.

Chapter 5 presents the conclusions, limitation of study and recommendations for future works.

CHAPTER 2

THEORY AND LITERATURE REVIEW

2.1 Discovery of Radiation

In 1895, Wilhelm Conrad Roentgen discovered a kind of invisible light and subsequently named it as X-rays. A year later in 1896, Sir Henri Becquerel found similar lights from uranium salts and named it as radioactive when he noticed this element continue transmitting by itself after many experiments. Marie Curie, who was a student of Sir Henri Becquerel became interested in this discovery and carried out further experiments where she later discovered other radioactive elements such as Polonium, Radium and Thorium. The discovery of X-rays initiated the idea for the medical world to use it for the observation of the internal structure of internal organs (Frame, 2004). Since its discovery, people were overly obsessed with radiation. In 1924, the approach of radioactive material as a radiotracer was first carried out in animals using Plumbum-210 and Bismuth-210. With the high confidence level, the Bismuth 214 was then used to evaluate blood flow rates in humans a year later (Reed, 2011). Since then, many more radiotracers such as Iodine-131, Cobalt-60, Technetium-99 and others have been discovered. Thus, this signalled the beginning of nuclear medicine era.

Although the discovery of radioactive elements provided the medical world with a new approach in many aspects, however, the radiation side effects resulting from the uncontrolled use has led to adverse effects. Industrial workers such as radium dial painters, were found to be suffering from bone cancer due to the accumulation of radiation exposure. Moreover, a number of workers in the medical line who were actively involved in X-ray work have been shown to suffer from leukemia and pernicious anaemia (Finch, 2007). Due to these incidences, the awareness towards radiation exposure from the use of radioactive materials have risen and affected the industry and healthcare.

2.2 Nuclear Medicine Introduction

Knowledge in healthcare growing up very fast, especially matters related to radiation. With the introduction of radiotracers, with the interest to study the internal structure has led to radiology, radiotheraphy and nuclear medicine. Nuclear medicine is one of medical branches which use a small amount of radioactive tracer to detect disease either for diagnostic or therapeutic purposes (Fahey, 2016). The radioactive tracer is a combination of radioisotope and pharmaceutical (drugs) that will be administered to the patient via injection, ingestion or inhalation. The radioactive tracer will enter the bloodstream and ends up to the problematic area and this can be detected when patient undergoes the imaging scan. The problematic area was visualised in nuclear medicine imaging tools when there was high uptake in the internal organs. Depending on the behaviour of the selected radiotracer, nuclear medicine imaging provides the information about the anatomy and physiology of the disease. Each radiotracer has its own targeted area. They will stay in the organ at certain time until it decayed physically

and biologically (Balasubramanian, 2016). Normally, only radioactive (radiotracer) with short half-life is used in nuclear medicine. This is very unique compared to other medical discipline. The most common radioisotopes used in nuclear medicine field for either diagnostic or therapeutic are Technecium-99, Iodine-125, Flourine-18, Iodine-124, Yttrium-90, and Iodine-131 (Saha, 2010).

The radiotracer was detected based on the (radiation) energy that emitted from the patient's body to the detector via collimator. The data was then transferred into electrical signal and visualised in image form. These images formed can be read by the physician based on the uptake distribution in internal organ of the patient. Nuclear medicine imaging has been proven as a great tool in the diagnostic and therapeutic of disease detection like tumour localization, kidney function, lung prefusion and thyroid. No surgical or biopsy was needed to gain the information on disease characteristic which makes nuclear medicine services safe and considered as one of the best alternative in medical lines.

2.2.1 Radionuclide and Radiopharmaceutical Production

Radiopharmaceutical 2-[18F] fluoro-2-deoxy-D-glucose (^{18}F-FDG) is a combination of radioisotope^{18}F and pharmaceutical drugs, FDG and is known as PET radiopharmaceutical (Wadsak & Mitterhauser, 2010). This is due to the nature of ^{18}F-FDG decay by emitting positron and most of the positron emitters have a short half-life like ^{18}F with 109.74 minutes.

Radioisotope ^{18}F is produced in a cyclotron. Cyclotron is a particle accelerator which accelerates protons in a spiral path (IAEA, 2012). The nuclear reaction can be

simplified as $^{18}O(p,n)^{18}F$. Accelerated high energy protons (H^+) entered the nucleus of high pressure enriched water of ^{18}O atom (target medium), and transformed it into radioisotopes ^{18}F by discharging a neutron (Strijckmans, 2001).

^{18}F-FDG can be used as a glucose-analogue and is the most current used tracer due to its versatility in glucose interaction detection (Fletcher et al., 2008; Cho et al., 2011). Tumour cell is categorized as an active cell which has high mitotic rate development. FDG accumulation is proportional to glucose utilisation. It responds to the consumption of glucose in cells as well as with hexokinase activity (R Boellaard et al., 2015). During normal glycolysis process, the glucose molecule is phosphorylated by hexokinase and undergoes a number of further enzymatic reactions for energy production. But when using the FDG, after the phosphorylation phase, it cannot proceed with further glycolysis process because of the different end form of glucose and will end up trapped in the cells until physical decay process occurs (Perng et al., 2015). Therefore, FDG PET has proven to be a sensitive imaging modality in differentiating between benign and malignant tissue (Damian et al., 2013).

Brain, kidney, urinary bladder and heart are the major organs in human. Data from previous study have shown that almost 15 - 20 % of the injected ^{18}F was eliminated by renal system or by pharmaco-kinetically within 16 minutes after receiving the injection, and 75 % were remained in the cells for physical decay (Staaf et al., 2012).

In the renal system pathway, the kidney is directly involved with other excretion organ such as urinary bladder. Is has been shown that due to the rapid elimination by renal system, this system contains high uptake of ^{18}F in the first hour. In normal patients,

low concentration of ^{18}F retains in the kidney and not enter the urinary bladder, so the patient will stay radioactive for some-while (Minamimoto et al., 2007).

Moreover, FDG PET has also been proven to be capable of detecting attenuation of cognitive in alzheimer disease and mild cognitive impairment based on measurement of glucose metabolism (Nobili & Morbelli, 2010; Cohen & Klunk, 2014).

2.2.2 Positron Emission Tomography-Computed Tomography (PET-CT) Hybrid Modality

Gamma camera is the main imaging tool in nuclear medicine procedures. What makes it different with other imaging scans is that it uses different scan techniques such as SPECT-CT and PET-CT. SPECT-CT system detects single photon while PET-CT detects dual positron energies that emits from the patient's body. This study involves only the PET-CT application.

2.2.2(a) Introduction

The detection of annihilation photons from positron emission decay process is the main element in PET-CT imaging technique (Sandip Basu et al., 2011). ^{18}F is an unstable atom due to having excess of protons in its atom. A proton in a nucleus of an atom is converted into a neutron and a positron. The positron is ejected together with neutrino.

Tissue cells are enriched with electrons. When positrons enter the tissue cell, it will have short lifetime and will quickly lose its kinetic energy during its travelling phase. Once the energy almost at rest momentum, it collides with other electron in the cells and become positronium (combination of positron and electron) about 10^{-10} s. After

that event, the annihilation process will take place (Sandip Basu et al., 2014). During the annihilation process, the energy of 1.022 MeV is released. This is based on Einstein's mass energy formula as:

$$E=mc^2 \qquad \text{(Eq. 2.1)}$$

where;

E is energy

m is mass

c is speed of light in vacuum

Two high energy photons emitted in opposite direction (180°) with energies of 511 keV are produced. These high kinetic energy photons have the ability to penetrate the body and hit the rings of the detector (crystal).

This interaction provides the detector with the signal and reacts by emitting visible light (scintillation light), and this is subsequently detected by photomultiplier tubes (PMT) and converted into an electrical current. The data are then collected and recorded as an acquisition data. Finally, the data is reconstructed (Phelps et al., 2006; Sandip Basu et al., 2014).

2.2.2(b) Principle of PET-CT Imaging

Acquisition data are collected from the coincidence events (referred to detected annihilation process). Only true coincidence events would be recorded where two detected annihilation photons of 180° apart originating from the same radioactive

decay and they interacted along the Line Of Response (LOR) (Fahey, 2002). But somehow other events like random and scattered events are also detectable by the detector and this needs to be first corrected to get the close image to radioactivity concentration (Kapoor et al., 2004).

The data are collected in different angles and radius of detector to complete the cross sectional of the images which refer to trans-axial and axial. The acquisition mode can be in two dimensional (2D) or in 3 dimensional (3D). 2D mode refers to the direct planes where recorded coincidence was within the LOR of the detector ring and 3D mode refers to the cross planes with an average amount of coincidence between few ring detectors. This will provide correct information of location and annihilation time (Fahey, 2002).

For 3D mode, data is collected in oblique LOR and it is more sensitive than the 2D acquisition (Lodge et al., 2006). The advantages of using 3D mode include minimising the patient scan time and reducing the amount of radioactivity injection (Nogueira et al., 2015).

Attenuation correction is referring to acquisition data that has been corrected. Software will remove the unwanted signal or noise such as from random and scattered events. This aims to obtain the result of tissue activity concentration value that represents the image volume. Attenuation correction can be performed either with direct measurement or calculation (Parker, 2005). Direct measurement refers to transmission scan and blank scan while calculations were based from assumption made on amount of attenuation from source outside will reflect the amount of attenuation inside with

constant attenuation correction, μ. Direct measurement is more accurate compared to the calculated method (Boellaard et al., 2015). In PET-CT studies, attenuation correction and scatter correction are performed using combination of CT transmission data and calculation method (Boellaard, 2009).

The scan images of the annihilation photon which detected and recorded in the raw data of PET will be reconstructed using the mathematical algorithms of computed tomography. The reconstruction method is important to convert the raw data which consist of the information on location of the annihilation takes place in the 2D or 3D images. These can be quantitatively detected reflecting the distribution of positron emitting radiopharmaceuticals in the scan object.

There are two main reconstruction methods used which are analytical or iterative, which referring to the filtered back-projection (FBP) or Ordered Subset Expectation Maximisation (OSEM), respectively (Sandip Basu et al., 2011). Filtered back-projection (FBP) uses the analytical method where it relates the lines integral measurement to the activity distribution in the object. As for the iterative method, it involves the statistical approach, and is known to be more quantitatively accurate than the analytical method. In the reconstruction techniques, multiple iteration steps were used to get a better reconstruction result which could indirectly minimise the artefact effect to the image. The image is then directly calculated in a single reconstruction step, so this makes the iterative method better compared to the FBP (A. Alessio & Kinahan, 2006).

The image can be displayed in Medical Interface Programme (MIP) and it is constructed in a 3D image view in trans-axial, coronal and sagittal planes. The CT images presented within grey and white area where it is based on tissue density (Cho et al., 2011). PET images is visualised in pseudo colour coding, where it guides the user to identify a particular activity concentration with different level of pseudo colour. Positron Emission Tomography is a great technique compared to Single Photon Emission to define each of the volume of element referred to concentration of radioactive tissue (Welch et al., 2013).

2.2.2(c) Standard Clinical Procedure of PET-CT Imaging

Clinical procedure begins with the patient preparation, followed by the procedure of scan until the patient is discharged. During patient preparation, the patient is counselled on diet one week prior to the date of appointment. Patient is advised to start fasting at least 4-6 hours before scan. However, they are allowed to drink only plain water and take their normal medicine. On the day of appointment, they must inform the staffs if they are likely to be pregnant, breastfeed, have drug allergy, claustrophobic and diabetes mellitus. Once they have passed the physical fitness examination, they are eligible to receive an injection of radiopharmaceutical and proceed with the PET-CT examination.

Small quantity of radioactive tracer ^{18}F-FDG will be injected into the vein of their hand or elbow. The dose was given based on body weight of 5 MBq kg^{-1}. There is no significant side effect as a result of this injection. After receiving an intravenous (IV) injection, patient needs to rest in the provided room approximately for 1 h (60 min). It is important that no physical activities such as unnecessary talking, chewing, eating or

any muscular or strenuous exercise as this may affect the result of the scan. Patient were asked to void the urine before proceed for PET-CT scan. This is important to minimise the scattered phenomenon in the body which can affect the image result i.e artefact images.

PET-CT scan procedure starts with a CT scan for two seconds which emits X-rays radiation followed by PET scan for approximately 20 to 30 min. It emits the gamma radiation which origin from positron annihilation process in the human body after injecting the radiopharmaceutical ^{18}F-FDG into the body before. The CT scan starts with a CT scout followed by CT helical for few seconds. The setting parameters for CT scout scan and CT helical scan are at voltage of 120 kVp, 100 mAs current, pitch at 0.8 and voltage of 140 kVp, current range of 10-100 mAs, pitch at 1.35, respectively as a standard clinical protocol for adult patient. Slightly different parameters are applied for the paediatric use. This machine is equipped with Automatic Exposure Control (AEC) function where the current and voltage was adjusted automatically based on tissue density.

2.2.2(d) Radiation Exposure Aspect In PET-CT

Patient underwent PET-CT imaging is exposed to dual radiation from the radiopharmaceutical ^{18}F-FDG (internal radiation) and the CT component that generates the X-rays radiation (external radiation). The CT effective dose depends on the applications, protocols and CT systems (Boellaard et al., 2015), while PET effective dose depends on radiopharmaceuticals, administered activity and weight of the patient (Gelfand, 2009). The risk of radiation exposure also depends on the patient's age. For instance, based on previous studies, children have been shown to be

more sensitive to radiation compared to adult (Kollek & Karwowska, 2009; Figueira et al., 2015).

However, radiation exposure can be reduced by adjusting the acquisition setting parameters such as tube current, tube voltage, filter, sinogram smoothing and clipping (Xia, 2012), crystal detector, setting of Full Width Half Maximum (FWHM) (Basu et al., 2011), as well as the reconstruction parameter (Vriens et al., 2010). Reconstruction settings (analytical versus iterative reconstruction, post-reconstruction filtering and image matrix size) could potentially influencing the quantification due to the effect of artefacts, noise levels and lesion size dependency (Vriens et al., 2010).

Besides that, they are also other factors that could contribute to patient dose reduction such as fasting blood glucose level, FDG uptake period, FDG distribution and clearance, patient motion (breathing) and patient discomfort (stress), which are all could influence the quantification, metal artifacs, glucose metabolism, and influence of attenuation correction (Vriens et al., 2010). Patient are recommended for pre-hydration plan to optimize the distribution of FDG throughout the body. This is important especially when involve a study on kidney and pelvic area (Lubberink et al., 2004; Coenen et al., 2010).

Automatic Exposure Control (AEC) technique is an alternative way to optimise the radiation dose exposure to the patient by giving the minimum CT dose to the patient (Mulkens et al., 2005). This technique applies the modification of CT tube current based on x,y and z planes according to the size and attenuation of the scanned body (McCollough et al., 2013). Greess et al., 2002 found that the CT exposure dose can be

reduced to 50% with the application of this technique, but the possibilities for heavy patient to receive higher exposure dose is there because the tube current needs to be increased to maintain the constant image noise.

2.3 Nuclear Medicine Dosimetry

Dosimetry or dose assessment is the calculation of the amount of deposited energy absorbed in tissue or organ that correlates with the radiation risk effect. This is important in order to evaluate radiation risk over benefits to the patient. Dose assessment in diagnostic is estimation using collective sample of population coefficient in calculation, while in therapeutic, the calculation is based on individual patient specific biokinetic. Dosimetry by calculation usually based on Monte Carlo simulation from developed phantom which already formed into computational software. While, dosimetry by measurement, which also known as external exposure where the assessment of dose based from the emitted radiation source outside the human body. However, people may have different views on dosimetry calculations due to some uncertainties factors.

Established organisations such as International Commission on Radiological Protection (ICRP), Medical Internal Radiation Dose (MIRD) and Radiation Dose Assessment Resource (RADAR) have established the fundamental concept in dosimetry such as quantities and units, equations, methods or techniques. All these efforts help to standardise the dosimetry result.

2.3.1 Quantities and Units

The International Commission on Radiation Units and Measurements (ICRU) has introduced the quantity measurement in radiation field that aim to assess the biological effects resulting from external and internal exposure to ionising radiation in terms of stochastic (cancer induction, genetic effects) as well as deterministic effects (tissue effects) in order to have sufficient mechanisms to control these effects.

2.3.1(a) Absorbed Dose, D

Absorbed dose is defined as a measurement on the amount of radiation energy absorbed in a target tissue per unit mass. The System International (S.I) unit is in Gray (Gy) where,

1 Gy = 1 J kg^{-1}

1 Gy = 100 rad

$$D = \frac{d\mathcal{E}}{dm} = 1 \text{ Gy} \qquad \text{(Eq. 2.2)}$$

In internal dosimetry calculation system, we assume the tissue has uniform distribution of radioactive material using a generic Equation 2.3:

$$D = \frac{k\,\tilde{A}\sum_i n_i\,E_i\,\phi_i}{m} \qquad \text{(Eq. 2.3)}$$

Where,

D is absorbed dose (rad or Gy)

Ã is cumulated activity (mCi-hr or MBq-sec)

n_i is number of radiations with energy,E emitted per nuclear transition

E_i is energy per radiation (MeV)

$ø_i$ is fraction of energy absorbed in the target

m is mass of target region (g or kg)

k is proportionality constant (rad-g/mCi-hr-MeV or Gy-kg/MBq-sec-MeV)

With S value formula :

$$S = \frac{k \sum_i n_i E_i \phi_i}{m} \qquad \text{(Eq. 2.4)}$$

MIRD has simplified the Equation 2.3 and 2.4:

$$D = \tilde{A}.S \qquad \text{(Eq. 2.5)}$$

where:

$\tilde{A}$ is the cumulated activity in source organ

S is S value derived from an appropriate phantom and Monte Carlo simulation

Absorbed fraction ϕ is fraction of radiation energy absorbed in a target organ per radiation energy emitted in the source organ. The value for absorb fraction is between $0.0 \leq \phi \leq 1.0$. Source organs have concentrations larger than the average body concentration depending on the source and target geometry (Monte Carlo method). In theory, the absorbed dose is dependents on the fraction of the administered activity in organ and rate of elimination from source organ.

Furthermore, there were authors or groups that have interest in developing the generic absorbed dose equation to another form. MIRD organisational use above Equation (2.4 and 2.5) in their calculation. While RADAR has modified the equation to be simpler in Equation 2.6:

$$D = N \times DF \qquad \text{(Eq. 2.6)}$$

Where,

N is number of disintegrations in the source

DF is dose factor

$$DF = \frac{k \sum_i n_i E_i \phi_i W_R}{m} \qquad \text{(Eq. 2.7)}$$

Where,

W_R is radiation weighting factor

The DF is written with the function of W_R which includes the use of a radiation-weighting factor, as defined by the International Commission on Radiological Protection (ICRP) (ICRP, 1991; Thorne, 1992). Fundamentally, the expression of S-value and Dose Factor (DF) are similar (Stabin et al., 2005).

2.3.1(b) Equivalent Dose, H_T

Equivalent dose is multiplied the absorbed dose with the radiation weighting factor, W_R to reflect the biological effect. Which has a relationship with the LET of different

types of radiation. The equivalent dose is used for radiological protection and suitable only for human estimation. The S.I unit is in Sievert (Sv).

1 Sv = 100 rem.

$$H_T = D.W_R \qquad \text{(Eq. 2.8)}$$

Where,

H_T is equivalent dose

D is absorbed dose

W_R is radiation weighting factor

2.3.1(c) Effective Dose, ED

Effective Dose is the product of equivalent dose weighted, H_T and tissue weighting factor, W_T. The tissue weighting factor reflects the risk or tissue harmless, while equivalent dose weighted for an organ or tissue is the proportion of the risk of stochastic effects to the total risk of stochastic effects when the whole body is irradiated uniformly. The examples of stochastic effects are cancer risk, life shortening and hereditary effects. The S.I unit is in Sievert (Sv).

1 Sv = 100 rem

$$ED = \Sigma_T H_T.W_T \qquad \text{(Eq. 2.9)}$$

where,

ED is effective dose

H_T is weighted equivalent dose

W_T is organ weighting factor which is $\Sigma_T W_T = 1.0$ in case of X-rays and Gamma-rays