ACCURACY OF ^{131}I ACTIVITY QUANTIFICATION AND DOSIMETRY IN THYROID PHANTOM USING 3D-IMAGE BASED SPECT/CT

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by

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LIST OF SYMBOLS

Ã	Cumulated Activity
Φ	Specific Absorbed Fraction
ϕ	Absorbed Fraction
τ	Residence Time
$U(t)$	Area under Uptake Curve on target
A(t)	Activity at time, t
D	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
UFOV	Useful field of view
CFOV	Central field of view

LIST OF ABBREVIATIONS

ALARA	As Low As Reasonably Achievable
ALI	Annual Limit on Intake
AMIDE	A Medical Imaging Data Examiner
CDR	Collimator Detector Response
C.F	Calibration Factor
CT	Computed Tomography
DF	Dose Factor
DLP	Dose Length Product
EPD	Electronic Pocket Dosimeter
FBP	Filtered Back Projection
FWHM	Full Width Half Maximum
IAEA	International Atomic Energy Agency
ICRP	International Commission on Radiological Protection
ICRU	International Commission on Radiation Units
IPPT	Institut Perubatan dan Pergigian Termaju
MIRD	Medical Internal Radiation Dose
OLINDA/EXM	Organ Level Internal Dosimetry Assessment / Exponential Modelling
OSEM	Ordered Subset Expectation Maximisation
OSL	Optically Stimulated Luminescence
PMT	Photomultiplier Tube
PVE	Partial Volume Effect
ROI	Region of Interest
SPECT/CT	Single Photon Emission Computed Tomography/Computed Tomography
TAC	Time Activity Curve
TLD	Thermoluminescent Dosimeter
VOI	Volume of Interest

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KETEPATAN KUANTIFIKASI AKTIVITI ^{131}I DAN DOSIMETRI DALAM FANTOM TIROID MENGGUNAKAN PENGIMEJAN BERASASKAN IMEJ 3D SPECT/CT

ABSTRAK

Pengimejan kuantitatif memberikan pemahaman yang lebih baik mengenai taburan radioaktiviti yang dapat digunakan dalam anggaran dos yang diserap pada organ sasaran tertentu. Tujuan kajian ini bagi mendapatkan ketepatan pengukuran dan dosimetri aktiviti ^{131}I dalam fantom tiroid menggunakan pengimejan SPECT/CT 3-dimensi (3D). Dalam kajian ini, satu siri pengimbasan SPECT/CT dijalankan terhadap fantom tiroid. Imej pelbagai saiz voxel 64, 128 dan 256 dengan beberapa bilangan iterasi dibina semula menggunakan aplikasi *ordered subsets expectation maximization*. Pengukuran aktiviti dalam fantom tiroid ditentukan dengan menggunakan perisian *Medical Image Data Examiner* berdasarkan nilai purata, maksimum, 0.7 maksimum dan 0.6 maksimum. Aktiviti terkumpul dalam fantom tiroid ditentukan oleh kawasan pengiraan di dalam lengkung aktiviti masa. Hasil kajian menunjukkan bahawa nilai purata bagi saiz voxel 128 dan 256 menunjukkan hasil yang tepat dengan ralat yang diperoleh antara 4.1% dan 18.2% sementara untuk nilai maksimum, ia memberikan kiraan yang melebihi had dengan ralat sehingga 78%. Aktiviti terkumpul yang diperoleh daripada SPECT/CT menunjukkan ralat sebanyak 15%. Hasil dosimetri organ dos terserap menggunakan dosimetri berdasarkan pengimejan 3D SPECT/CT adalah 16.1% lebih rendah daripada ukuran dos terserap menggunakan dosimeter pendarkilau ransangan optik (OSL). Kajian ini menunjukkan bahawa pengimejan berasaskan 3-D SPECT/ CT dengan ketepatan kuantifikasi yang baik mampu menganggarkan organ dos terserap dalam terapi^{131}I.

ACCURACY OF ^{131}I ACTIVITY QUANTIFICATION AND DOSIMETRY IN THYROID PHANTOM USING 3D- IMAGED BASE SPECT/CT

ABSTRACT

Quantitative imaging gives a better understanding of the distribution of radioactivity that can be used in the estimation of absorbed dose in the specific target organ. The goal of this study was to obtain the accuracy of ^{131}I activity quantification and dosimetry in thyroid uptake phantom using 3-dimensional (3D) SPECT/CT imaging. In this study, a series of SPECT/CT acquisitions of the thyroid uptake was performed. Images of different voxel sizes 64, 128, and 256 with several iterations numbers were reconstructed using ordered-subsets expectation maximization (OSEM). The quantification of the activity in the phantom was determined using a Medical Image Data Examiner (AMIDE) software based on the mean, maximum, 0.7 maximum and 0.6 maximum value. The cumulated activity in the phantom was determined by the calculating area under the curve (AUC) in the time-activity curve. The results showed that the mean value of 128 and 256 voxel show a better result with the error obtained between 4.1% and 18.2% whereas for the maximum value, it gives an overestimate count with the error up to 78%. The cumulated activity derived from SPECT/CT showed an error margin of 15%. The dosimetry result of organ absorbed dose using 3D imaged based dosimetry was approximately 16.1% lower than the absorbed dose measure using Optical Stimulated Luminescence (OSL) dosimeter. This research shows that the 3D image based SPECT/CT with good quantification accuracy capable of estimating organ absorbed dose in^{131}I therapy.

CHAPTER 1

INTRODUCTION

1.1 Background

Radionuclide therapy was proposed in the 1940s, where it used radioactive iodine isotopes to control hyperthyroidism or to even destroy the differentiated thyroid cancer (DTC) cells (Ljungberg & Gleisner, 2015). The use of ^{131}I in the diagnostic and therapy for thyroid abnormality in nuclear medicine is still relevant even when a very significant discovery of new radiopharmaceutical is still undergoing. The expansion of the clinical indications is due to the development of new radio-labeled compounds as well as the evidence of the response to the therapy in the random clinical trials, for instance the use of somatostatin ^{177}Lu analogs for neuroendocrine tumors (Cives & Strosberg, 2017) and ^{223}Ra for bone metastases of prostate carcinoma (Parker et al., 2013).

In both nuclear medicine and radiotherapy, ionizing radiation has been used for diagnostic and therapeutic purposes. Therefore, it should be emphasized that the radiopharmaceuticals given to patients are unsealed sources, which will cause a wide distribution of radioactive and metabolic interactions in the patient's body. Radiopharmaceuticals are made up of chemical compounds (drug) that were tagged with a radioisotope and then it will exhibit extensive biological exchange in the organism due to their variable affinity for binding sites and the excretion pathways. Thus, due to this pharmacokinetic behavior of the radiopharmaceuticals, it leads to difficulty in determining the residence time.

Most radionuclides used in radiotherapy will emit particles with low penetration power (in a range allowed) and high linear energy transfer (LET), resulting in high ionisation in the uptakes site (Kumar et al., 2016). Meanwhile, in some other situations, radionuclides that emit gamma rays will be in use, where these types of radionuclides have high penetration power, which can allow external detection and result in the imaging of the radiopharmaceutical biodistribution in the patient's body. Radioisotope imaging that was obtained by planar scintigraphy, single photon emission computed tomography (SPECT) and positron emission tomography (PET) scans are essential in determining the radiation dose at a specific target organ or tumor. Other than that, the measurement of blood samples or whole–body detection can also be used to estimate the radiation dose in the bone marrow but this is less meaningful for the dosimetry of localized structures, such as tumors (Willegaignon et al., 2012) and other organs.

The treatment for DTC by using radioactive iodine is a standard procedure in removing the remnant thyroid tissues after the removal surgery and it is also used for the treatment of iodine - avid metastases. There was a broad range of fixed activities of ^{131}I recommended being used for this purpose. For instance, in many cases, an activity between 1.1 and 3.7 GBq was prescribed for the first treatment therapy right after thyroidectomy in a newly diagnosed DTC to remove the remaining glandular tissues (Hänscheid et al., 2006). Thus, the main disadvantage of using a fixed activity is the failure to consider the optimum dose required for an individual patient. For example, the optimal activity of radioiodine prescribed to metastatic thyroid carcinoma patients should be balanced between the minimum amount of radioiodine that will deliver a lethal of radiation dose to the entire lesion or metastasis while minimizing side effects to other critical organs such as the kidney, spleen, liver and bone marrow.

Due to this natural fixed activities of the radionuclide, the minimal radioiodine activity that can deliver a lethal dose cannot be determined as well as the maximum allowable reasonably safe absorbed dose. Other than that, fixed activities that was recommended seem to be inequivalent to the same amount of the radioiodine absorbed dose that was calculated by dosimetry at a given time (Willegaignon et al., 2012). As the dose rate is a vital key in radionuclides therapy (RNT), administering multiple similar small amounts of doses may give lesser benefit than the same total amount of doses given at the time (Lassmann et al., 2010). In addition, the non – lethal doses administered previously may cause reduced effectiveness of the subsequent doses given to the patients (Medvedec, 2005). Thus, due to this major reason, it is a very good choice to choose the dosimetry–based approach rather than the conventional fixed activity regime, which will allow the administered therapeutic activity to be increased while avoiding the undesired burden to other sensitive organs. Therefore, the fixed-dose technique can reduce the potential toxicity as well as optimise the absorbed dose of the remnant tissues.

There are multiple techniques adopted to determine the radiation dose to the patients with DTC. Previously, the thyroid probe technique was widely used but with a drawback of the lack of accuracy in estimating the true activity that accumulated to the thyroid. The current standard for the quantitative imaging procedure was divided into 2–Dimensional (2D) and 3–Dimensional (3D). Meanwhile in 2D planar imaging, the final image reconstructed is based on the 2D projection of an overlap structure. This is resulted due to the fact that the signal at a specific location in the image is built up from the photons emitted along the projection line. Therefore, if a specific structure organ is the point of focus, the photons emitted can also come from the over- and underlying activity along the projection lines. Consequently, the sensitivity to detect

small lesion will be lessened and significant reduction of image contrast will be observed (Ljungberg & Gleisner, 2016). Thus, in the previous studies it is reported that the accuracy in organ activity from the 2D imaging is immensely variable; as to whether it is overestimating or underestimating the error of the activity, it could be up to 50% or higher (He & Frey, 2006).

By using SPECT, 3D spatial information will be provided and thus solve the organ overlap issues and also increase the contrast between the target organ and the background. Therefore, it is a crucial step in enabling the 3D SPECT/CT based dosimetry. Furthermore, in modern hybrid SPECT/CT scanner, an improvement of attenuation and localization by CT leads to better organ delineation in targeted radionuclide therapy (Li et al., 2017). The absorbed dose calculation in 3D dosimetry was greatly influenced by the SPECT activity quantification and also the image quality. Thus, it is important to have an accurate SPECT/CT reconstruction by emphasizing the scatter, attenuation and the collimator detector response (CDR) as well as the optimum choice of iteration number and the calibration procedure. Besides that, the size of the projection – image is another aspect that should be selected by considering the suitable trade off of the image noise and spatial resolution.

A phantom study was conducted by using 3D Ordered Subset Expectation Maximisation (OSEM) reconstruction in SPECT/CT system by applying the correction scatter, attenuation and resolution. For target sizes smaller than 16 mL, the estimated dose accuracy within 12% of error was achieved from a 3D Monte Carlo calculation (Dewaraja et al., 2010). A study conducted by Shcherbinin et al in 2008 demonstrated that the quantification accuracy for target size at 32 mL was smaller than 5% with the expectation of the quantification accuracy to be approximately 10% for

almost all the organs and lesions and larger error are to be expected for volumes with dimensions smaller than the SPECT image resolution (Shcherbinin et al., 2008).

The internal radiation dosimetry in nuclear medicine was commonly related to the estimation of the amount of radionuclides and the distribution of radiation energy that the radionuclides deposited in the tissues. It had been used to determine the absorbed dose and other related quantities for radiation protection, risk management and treatment planning purposes. A method was developed to estimate the absorbed dose in a target organ and it is called Medical Internal Radiation Dosimetry (MIRD). In the MIRD method, it depends on the decay of the radioactivity in the target organ, the amount of energy deposited in the target organ by the source, the administered activity, mass of the target organ, and the residence time. While the residence time is a vital parameter in the MIRD calculation, it can be obtained by dividing the accumulated activity in a time-activity curve with the initial activity (Bolch et al., 2009).

An advancement in internal dosimetry has been increasing rapidly over the years. Guidelines in performing internal dosimetry were provided by the committee that was related to the protection of radiation such as the International Commission on Radiological Protection (ICRP), the Medical Internal Radiation Dose (MIRD), as well as the Radiation Dose Assessment Resource (RADAR). These guidelines were provided to regulate the radiation received by a person that works with radiation as well as the exposure dose by the patient. Thus, as they can gather all the information, they can provide a radiation dosimetry handbook that begins with the data collection of the patients who underwent any nuclear medicine examination until the result analysis. Other than that, this committee also developed the mathematical modeling

software such as Medical Internal Radiation Dose (MIRDOSE), Simulation De Dose (SIMDOSE), and Organ Level Internal Dosimetry Assessment or Exponential Modelling (OLINDA or EXM) for calculating the patient dose that was well accepted worldwide (Fernald, 2015).

1.2 Problem statement

In general, a conventional 2D planar imaging method had been performed worldwide in order to estimate the dose for RNT. Nevertheless, due to its limited quantitative accuracy in estimating the radionuclide distribution, this leads to inaccuracy in estimating the radionuclide's accumulated activity within the body (Li et al., 2017). In Nuclear Medicine, accurate image quantification had always been an issue and it is not only an issue in the context of the dose calculation. Therefore, many other studies had been done in order to focus on improving the quantitative accuracy in SPECT and also in PET in the area of attenuation correction, scatter correction, compensation of the detector response function, motion compensation and partial volume effect correction (Li et al., 2017). The methods developed had been available in the latest software associated with SPECT imaging (Flux et al., 2017).

Meanwhile, in 3D SPECT imaging, the objective is to measure the radioactivity within a target volume in an absolute unit such as Becquerels. The ^{131}I quantification accuracy can be improved impressively by using the iterative reconstruction method. This is included by compensating the non – homogenous attenuation, scatter and CDR (Van Gils et al., 2016). Thus, a hybrid imaging system such as SPECT/CT with a physical compensation give the accuracy result to the organ of interest in internal emitter therapy application within 10%-15%. (Yuni K Dewaraja et al., 2013).

There was no existing standard method for performing internal dosimetry or for assessing the uncertainties inherent in the dosimetric calculation (Gear et al., 2007). In 2018, it was suggested that a comprehensive analysis of uncertainty propagation inherent in every aspect of the dosimetry calculation needs to be obtained and used in nuclear medicine (NM) centers where radionuclide therapy is carried out (Gear et al., 2018). Thus, to sort out the situation, a study of the accuracy of activity quantification and absorbed dose using the 3D SPECT/CT image-based method should be conducted.

1.3 Objective of the study

This study's objective is to determine the radiation dose in thyroid phantom using 3D SPECT/CT image-based dosimetry.

The specific objectives are listed below:

i. To optimise the activity quantification of ^{131}I based on matrix size, quantification metric and iteration number.

ii. To measure and validate the accuracy of the activity of ^{131}I in the thyroid phantom using 3D imaged- based dosimetry SPECT/CT.

iii. To estimate the absorbed dose using image-based dosimetry based on MIRD principle and compare it with optically stimulated luminescence (OSL) using thyroid phantom.

1.4 Significance of the study

This study's findings will provide us with the accuracy of the 3D image-based dosimetry methods compared to the external radiation dose monitoring using OSL. This advance imaging method will enhance the efficiency in delivery the thyroid tumor dose to the patients in a clinical setup.

1.5 Scope of study

This study involves 3D imaging techniques to obtain ^{131}I radiation doses in the thyroid phantom with SPECT/CT modality. As many factors influence the uncertainties in image-based 3D dosimetry, it is very important to identify the amplitude and potential sources of errors for the final dose calculation of the tumors and critical organs in the patient body. This study focuses on three different parameters that will affect the accuracy of dose calculation, namely the matrix size, iteration number during the OSEM reconstruction process, and the quantitative analysis metric such as mean and maximum.

The AMIDE software was used in analysing the image and OLINDA/EXM was used for dose estimation per unit administered activity. Hence, the findings of this study will provide us the accuracy of the 3D image-based on the dosimetry methods compared to the external radiation dose monitoring using OSL. This advanced imaging method will be beneficial in enhancing the patient-specific dose thyroid tumor-dosimetry calculation in a clinical setup.

1.6 Outline of study

This thesis consists of five chapters.

Chapter one introduce the background and brief on the purposes of 3D image-based dosimetry and dose validation in thyroid phantom. It also discusses the advantages of performing therapeutic individualised personal dosimetry in Nuclear Medicine and the importance of dose evaluation and risk assessment to the patient.

Meanwhile, in chapter two, a discussion about previous studies concerning the quantification of images on the SPECT/CT imaging was done in the literature. A theory about the principle of SPECT/CT imaging was also discussed, as the properties and function of radionuclide ^{131}I are crucial to obtain the optimum result in thyroid treatment. To obtain the radiation dose, the method of internal dosimetry analysis and calculation and external dosimetry using OSL were also discussed in this chapter.

Next, in chapter three, the materials and the methodology used in this study are going to be described. In determining the radiation dose, the application of various analyzing software such as Medical Image Data Examiner (AMIDE) and Organ INternal Dose Assessment/ EXponential Modelling (OLINDA/EXM) also the OSL nanodot for external dosimetry method are also described.

In chapter 4, the results and also discussions from this study are going to be presented. These studies' results are divided into two parts, wherein part one, the establishment of the optimum parameter for image quantification in SPECT/CT image is based on the MIRD technique. In part two, the determination of radiation dose is based on MIRD internal dosimetry from SPECT/CT images and external dosimetry from OSL nanodots. All the results obtained are presented in graphs and tables format to ensure a detailed analysis and explanation in the discussion section.

In chapter 5, the author presents the conclusion and recommendations for some avenues for future studies.

CHAPTER 2
LITERATURE REVIEW

2.1 Quantitative Imaging in Nuclear Medicine

Determining the SPECT reconstruction parameter is a vital move in acquiring a valid and accurate quantification result. Hence, it will be usable in the clinical dosimetry analysis (Frey et al., 2012). In determining the optimum iteration number for ^{131}I radionuclide therapy, Dewaraja et al. (2010) used a clinically voxel-phantom that was inserted with 1 GBq of ^{131}I. SPECT reconstruction was performed using OSEM with the compensation for attenuation, 3D detector response and scatter. Thus, the result obtained shows that an increase in the number of iterations can improve the recovery count, but it will also increase the noise. To improve the quantification activity, a large number of iterations was used, but this depends on the capabilities of the computer system. Based on the study performed, the iteration numbers for all reconstruction stopping point are 60.

In 2016, Van Gils et al. had studied the impact of scatter correction and collimator–detector response (CDR) parameters. In this study, a NEMA 2001/ IEC 1998 body phantom with a background ratio of 10:1 was used, and the total activity recorded of ^{131}I is 1.6 GBq. Then, OSEM with window-based scatter correction, several CDR models, and a Monte Carlo Simulator was used to reconstruct the image. Thus, from the study performed, they learned that by using the Monte Carlo method for scattered correction, it had given them a better accuracy in the phantom activity quantification rather than that triple energy window (TEW). The results obtained show that the relative error presence between SPECT quantification and the dose calibrator is less than 1%, 26%, and 33%. Other than that, in all measured spherical and lung parameters, the lowest performance in the measurement was shown when CDR was not applied in the

SPECT quantification. This indicates that the accuracy of the CDR can affect the quantification of cold and hot lesions, which also happens to the lung insert in the reconstructed images.

Other than that, rather than using the reconstruction parameter, a study conducted by Kappadath in 2011 suggests that the tomography projection can also affect the accuracy of the SPECT quantification. From the study performed by Kappadath, the SPECT/CT system with different matrix sizes each of 256 x 256, 128 x 128 and 64 x 64 required eight scans of coplanar point sources, which the sizes of the point sources smaller than 1 mm^3 that consist of high concentration of ^{99m}Tc solution, where each gives the result of 0.9 mm^3, 1.8 mm^3, and 3.6 mm^3 voxel size respectively. In each point source, the radial and tangential profile in reconstructed SPECT images, the SPECT spatial resolution was estimated as the Full Width at Half Maximum (FWHM). **Figure 2.1** shows that with smaller voxel sizes, both radial and tangential resolution can be improved. Other than that, the decline of the resolution of the SPECT images can also be due to the size of the voxels, whereby the larger the size, the poorer the resolution. Thus, this will cause inaccuracy in evaluating the absorbed dose distribution in tumors that are smaller than the SPECT resolution.

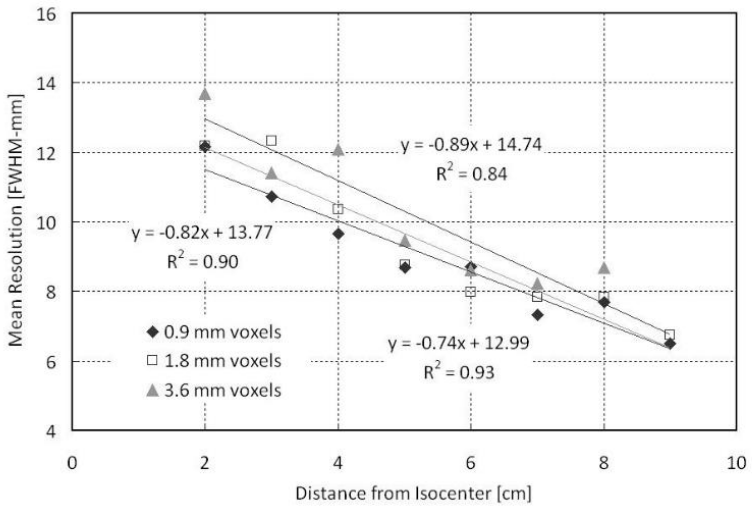

Figure 2.1 The mean resolution for point sources and their linear fits plotted versus radial distance from isocentre with different SPECT voxel sizes

2.2 Personalized dosimetry in ^{131}I

In the application of radionuclides in the patients for therapy, a dosimetry-based approach was applied rather than the fixed-dose regime. This is because the dosimetry-based method can eliminate the challenge of the inherent conventional fixed-dose regimen. This challenge is presented when the disease is already at the advanced stage. This is because at the advanced stage, the cancer cells can already improve their resistance toward the therapy given, thus to have a successful treatment, the dose needs to be larger than the dose given to the patient in the last treatment (Verburg et al., 2017). That said, the increase of the dose can cause the organ to be exposed to the risk of radiation toxicity. Following that, according to Wierts et al., (2016), due to the absence of the radiation toxicity (by using the fixed-dose regimen), it can cause under treatment, as the administered dose of ^{131}I is lower than needed

Other than that, the radiation dosimetry regime also has the potential to increase the effectiveness of iodine therapy and as well as to prevent or better limit the toxicity

to the healthy tissues. For example, in metastatic disease therapy, the use of effective Radioiodine (RAI) activity is crucial. However, the sufficient dose level required to have an effective metastatic target treatment is very complicated to achieve. This is because the radiation exposure level to sensitive tissue such as bone marrow cannot be tolerated. Nevertheless, by using the RAI, the target tissues can be directly approached by radionuclides. Also, almost all Neuroendocrine Tumor (NET) are very sensitive to radiation, thus delivering an adequate amount of dose to those tumors without planning, which can cause damage to the neighbouring healthy tissues around the tumor (Gargavij et al., 2010). Other than that, the treatment for the B – cell lymphoma and those radiosensitive tissues are always in need to have improvement, which will later provide the rationale towards the application of systemic radiotherapy (Rizvi et al., 2012). Meanwhile, in radioimmunotherapy (RIT), it is justifiable to apply individualized dosimetry with ^{131}I labeled rituximab referring to the vast difference of organ absorbed dose among the patients (Muylle et al., 2015).

Meanwhile, for the standard fixed–dose regime, it was applied due to the limitation of the tools to calculate the individual doses, which means that the same doses were given to every patient who required the same treatment. However, with the latest technology developed, which can provide individual doses to each patient, there is a need to improvise the treatment to have a better result and better outcome. Other than that, there is a large body of evidence in the literature these days, which shows the improvement of treatment outcome with the use of the patient-specific dosimetry rather than the fixed-dose therapy regimen (Michael G. Stabin, 2016). For instance, the ^{131}I therapeutic method is said to be one of those therapies in which the patient-specific treatment planning regime are increasing in number (Gear et al., 2018).

2.3 SPECT Quantification

Image quantification is a process that has been carried out by using a computational mean to obtain a set of numbers that explained the condition of the images acquired. This image quantification can be divided into two different quantification, which is relative quantification and absolute quantification. Thus, to have the accurate calculation of absorbed dose and accurate evaluation of the treatment outcome (after the comparison of the image between before and after therapy), accurate image quantification is needed as the prior condition. Although a simple quantitative measurement can be carried out for the planar images, it was limited by its lack of depth information about the image. Thus, it is pronounced that the accurate quantification of the 3 – D images of the SPECT is required.

2.3.1 Relative quantification

Between relative quantification and absolute quantification, relative quantification is a lot easier than absolute quantification. This is because relative quantification is less meticulous than absolute quantification. Relative quantification only requires the information derived from the image count without converting the count to the activity or is neither needed to apply any correction to the image. Usually, relative quantification is used to compare the distribution of the radioactivity between two sets of data. Other than that, relative quantification can also compare two data sets between the healthy organ image and the abnormal one. For example, relative quantification was done on two images to compare the stress and rest ventricle of an adult with the possibility of having ischemia.

2.3.2 Absolute quantification

Absolute quantification is a process of determining radioactivity concentration at any specific region of interest (ROI) in the nuclear medicine image, which is reliable in reflecting the concentration of the activity in the object's image. To acquire the data by the absolute quantification method, several factors that can affect the image quantification need to be applied. This step is necessary to convert the counts to activity accurately using a predetermined calibration factor (CF). Therefore, absolute quantification is useful regarding the total activity in the area, the volume defined in the image, and the detail about the activity distribution (Shcherbinin & Celler, 2010).

Using absolute quantification in SPECT is to precisely recover the 3-D activity distribution in the NM images. Other than that, by using this absolute quantification, a better diagnostic and therapeutic judgment can be made using these images (Frey et al., 2012). Therefore, by improving the quality and the quantity of the data, it is much possible to have the best accuracy. To improve the quality and the quantity of the data, the data must be acquired during the formation process and the image degrading factors must be corrected during the image reconstruction process.

2.3.2(a) Volume delineation

Thresholding is one of the methods used in the image segmentation (Grimes et al., 2012). By the thresholding principle, the voxels with counts more than the threshold value will be considered as the voxels of the target object. Threshold values can be determined using fixed, adaptive, and iterative thresholding methods. A previous study has shown that the iterative thresholding method is the most accurate method to estimate the volume (Velo & Zakaria, 2015).

For instance, to have an accurate delineation of the SPECT images thyroid organs, the 3–D isocontour volume delineation tool called AMIDE (Loening & Gambhir, 2003) was used where it follows the threshold method. The 3 – D isocontour can be explained as the neighbouring value, whether a value can be at an absolute minimum or maximum or in between the minimum and the maximum. This threshold method also allows for the modification of the VOI that can fit perfectly according to the shape of the object of interest. For a sphere, the ellipsoid VOI had been used to define the geometric sphere sizes. Other than that, this tool can also be used to specify a diameter for each x, y and z-direction and in special cases, where x = y = z.

2.3.2(b) Calibration factor

In absolute quantification, the CF is used to convert the reconstructed SPECT counts to activity by assuming that the activity is known. The CF unit is cps/MBq. Then, the tumor and organ activity maps can be acquired by dividing the image counts from the reconstructed SPECT images with the predetermined CF after the CF had been determined (Peters et al., 2019). Equation 2.5 shows the equation of the absolute quantification CF.

$$\mathrm{CF}\left[\frac{\mathrm{cps/ml}}{\mathrm{kBq/ml}}\right] = \frac{\left(\frac{\mu}{\mathrm{t.n.v}}\right)}{\mathrm{A}} \qquad \text{(Eq.2.5)}$$

Where,

μ is the mean voxel value in the reconstructed image

t is the time per projection, n is the number of projections

ν is the voxel size

A is the actual activity concentration in the phantom

2.3.3 Factors Influencing Accuracy in SPECT Quantification

2.3.3(a) Attenuation

Attenuation is a process of reducing the number of detected photons during image formation. This attenuation process can occur in two different places namely inside the patient's body and at the surface of the collimator. In SPECT image formation, the attenuation that occurs at a deeper location within the patient's body could significantly impact the structure of the image, which means that photon attenuation in SPECT is depth-dependent. Then, if the photons did escape, the attenuation that occurs within the patient's body would eventually be attenuated at the collimator's surface, then it would subsequently degrade the image that will be formed. For the attenuation without correction, the activity of the ROI will appear hotter, closer to the detector. Meanwhile, the activity of the ROI will appear colder if its position is far away from the detector. Therefore, the attenuation correction mechanism plays an important role to remove the artifacts in order to get optimum image quality.

Therefore, it is easy to say that the photons' attenuation's effect could give upon the SPECT images as one of the limitations and this photon attenuation needs to be corrected. Other than that, if the target object is large, this photon attenuation could become the single largest factor that will cause the quantitative accuracy to be degraded.

2.3.3(b) Scatter

When the scattered photons are taken into consideration in the image formation, the spatial resolution, the image contrast and the quantification accuracy would be degrading (Pereira et al., 2010). The scattered photons pass through the collimator and get captured by the gamma camera. Then, it will be considered as incoming points from

the image object (which is the direction of the photons in line with the collimator holes). If the final image is reconstructed with the attenuation compensation without the scatter correction, a false increase of the image intensity will be notified. Some of the factors that determine the magnitude of photon scattering include the energy window setting, photons energy, source depth, and the system's energy resolution. The scatter effect could become more significant for photons with higher energy and also for the radionuclides that have multiphoton emission at the same time.

2.3.3(c) Collimator Detector Response (CDR)

The collimator detector response (CDR) 's primary function is to compensate for the image resolution loss and it consists of four parameters. The four parameters are intrinsic response, geometric response, septal scatter and septal penetration, described in **Figure 2.2** (Philipp Ritt et al., 2011). The first parameter is the intrinsic response, which would describe the effect of the photon interaction in the detector system without the collimator's presence. This includes the photons scattering and the statistical uncertainty in the photon origin estimation. However, this intrinsic response is limited by the crystal resolution and the accuracy of the position. The second parameter is the geometric response, in which this geometric response represents the effect of the source to the collimator. This is because the response measured in the crystal depends on the source to collimator distance, which is due to absorptive parallel – hole collimation of the photons. Lastly, the third and fourth parameters are septal scatter and septal penetration. This septal scatter and penetration are those components of CDR that correspond to the photons that pass through the collimator septa, causing the spatial resolution to degrade. However, the effects of these septal scatter and penetration are crucial for the gamma rays with medium and high energy.

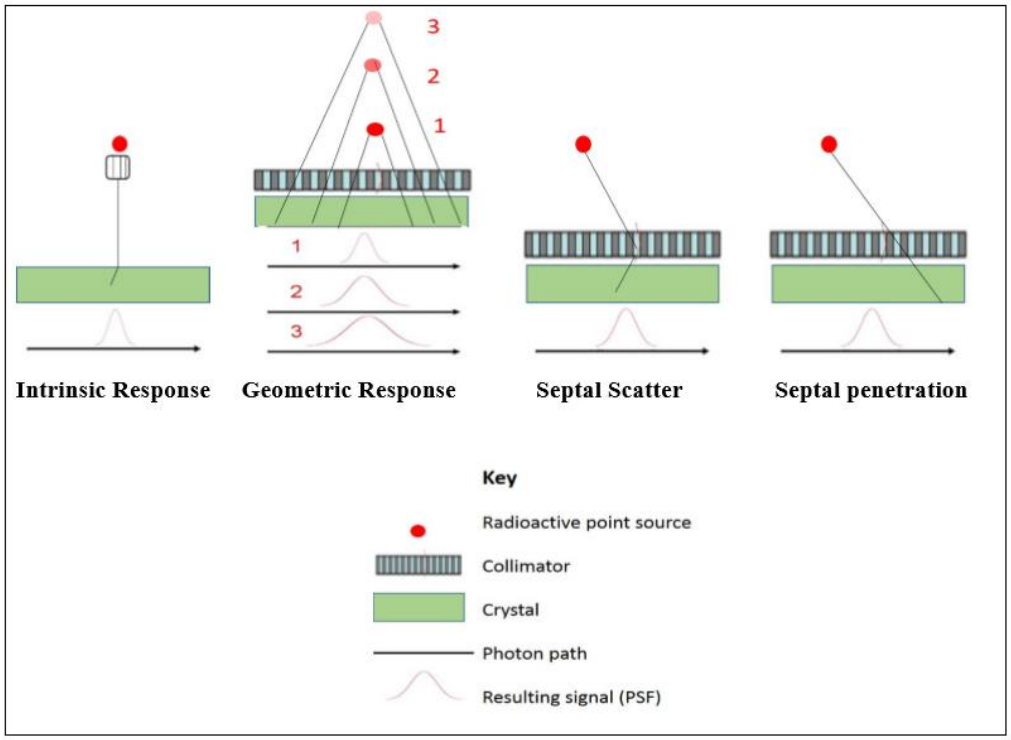

Figure 2.2 Four different responses of CDR in SPECT (Philipp Ritt et al., 2011)

2.3.3(d) Partial Volume Effect (PVE)

Partial volume effect (PVE) is one of the main factors that could affect the SPECT quantification image accuracy. There are two factors combined that can cause PVE in nuclear medicine images. The first factor that could contribute to PVE is image sampling. The presence of this factor is due to the difficulty of achieving organ delineation. This difficulty can occur as each of the SPECT voxels comes with a 3 – D cubical shape and in a certain size. Thus, due to this difficulty of delineating the organ of interest, it will eventually lead to the difficulty in acquiring the accurate values of the activity concentration at the organ boundaries, as the activity was assumed to be uniformly distributed throughout the voxels.

Meanwhile, the second factor is the limited spatial resolution of the SPECT imaging system. The image blur is introduced by limited spatial resolution, and the

signal coming from a point source will be detected not only in one pixel, but also in neighbouring pixels (Frey et al., 2012). When considering a functional structure of interest, part of the structure's activity will also be detected outside a VOI drawn around the structure. The measured activity may be underestimated when the source activity is distributed over the ROI borders due to spill-out effects. On the contrary, spill-in effects occur when activity originating from outside the studied structure leaks into the ROI, increasing the counts measured, resulting in an overestimation of activity (Ljungberg, 2018). **Figure 2.3** below shows the illustration of spill-out and spill-in PV effects.

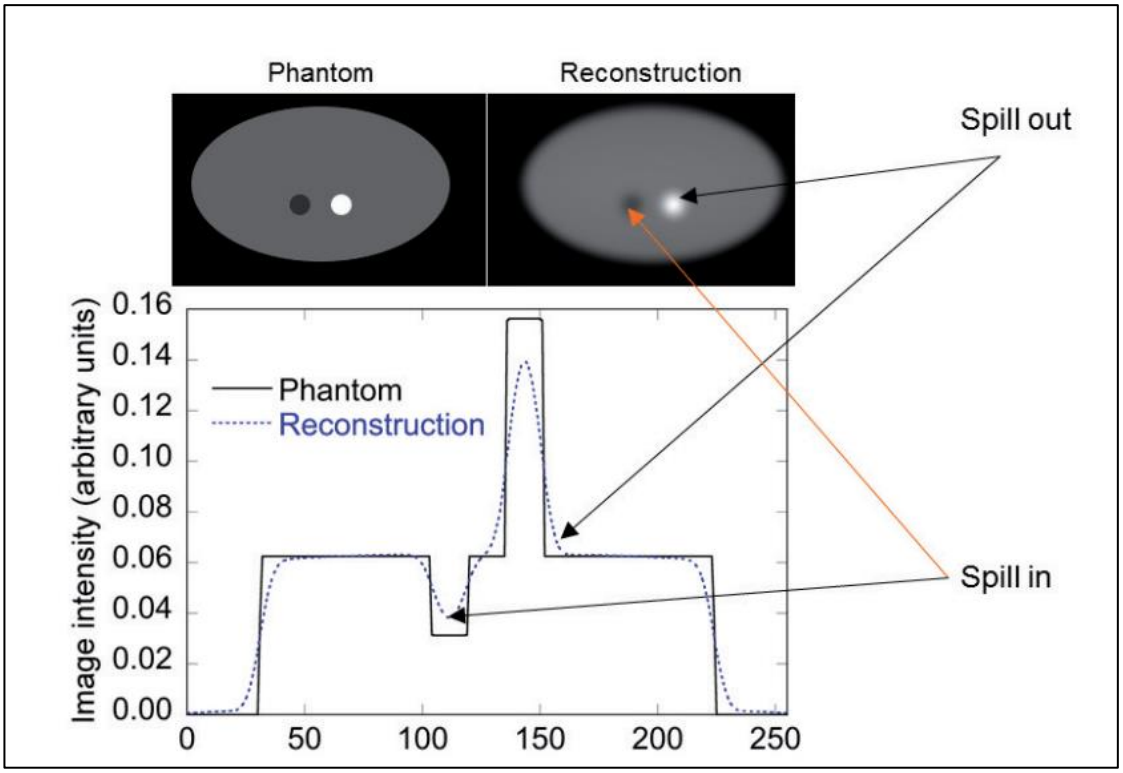

Figure 2.3 Illustration of spill-out and spill-in PV effects. Spill-out results in estimating reduced activity in a region that has higher activity than its surroundings; spill-in results in overestimating the activity in a region that has lower activity than its surroundings. (IAEA , 2014)

2.3.3(e) Size of the voxel

Voxel sizes is one of the parameters that could affect the SPECT image quantification. Therefore, it is recommended to use a smaller voxel because it can improve the accuracy of the image quantification, which subsequently improves the VOI definition (Sjögreen et al., 2009). In addition, if the misdefinition of the ROI occurs, it will directly affect the number of pixels included inside the object. Thus, it is safe to state that the accuracy of the SPECT quantification depends on the count of the pixels per ROI.

2.4 Dosimetry in Nuclear Medicine

Dosimetry is defined as calculating the amount of deposited energy absorbed in tissues and organs that corresponds to the radiation risk effect. Dosimetry is essential in nuclear medicine as it is used to assess the radiation risk over the benefit that could happen to the patient. Other than that, dose assessment in nuclear medicine refers to the dosimetry of the radionuclides distributed internally (Ljungberg and Sjögreen Gleisner, 2016). The dose assessment's objective is to determine the radiation energy that had been deposited (by internal radiation source) in the different parts of the human body. Therefore, due to the dose assessment, it can evaluate the risk and benefit of the different diagnostics and therapeutic procedures as much as possible.

This dosimetry can be carried out either by calculation or measurement. Dosimetry by calculation is based on the Monte Carlo simulation of the developed phantom, which is computational software. In contrast, dosimetry by measurement is the assessment of the dose of radiation that was emitted outside the human body, which is also known as external exposure.

Therefore, to standardize the dosimetry, a lot of established organizations related to the radiation protection system such as the ICRP, MIRD and RADAR had established a fundamental concept of the dosimetry. An instance would be the quantities and units of the radiation, equations to calculate the dosimetry and method to assess the external radiation exposure.

2.4.1 Radiation quantities and units

The International Commission on Radiation Units and Measurement (ICRU) had established the quantity of measurement in the radiation field. This quantity measurement was then utilized to assess the biological effect after being exposed to ionizing radiation, either internally or externally. These biological effects could be in terms of the stochastic effect or deterministic effect. Therefore, by applying this assessment, at least a sufficient mechanism could be built to control these effects.

2.4.1(a) Absorbed dose (D)

The absorbed dose (D) is defined as the statistical average of the energy (*E*) imparted per unit mass at a matter:

$$D = \frac{d\mathcal{E}}{dm} \qquad \text{(Eq. 2.6)}$$

The absorbed dose unit is the Gray (Gy) and one Gy is equal to 1 joule of energy absorbed per kilogram of matter (1 J/kg). The concept of absorbed dose applies to all materials and types of ionizing radiation.

Other than that, in MIRD formalism, the absorbed dose in the selected organ can be determined using the equation below:

$$D = \frac{k\,\tilde{A}\sum_i n_i\,E_i\,\phi_i}{m} \qquad \text{(Eq. 2.7)}$$

Where,

D is an organ absorbed dose in (Gy)

Ã is cumulated activity (MBq-sec)

n_i is the frequency of the radiation with energy, E(MeV) emitted per nuclear transition

E_i is energy per radiation (MeV)

$ø_i$ is the absorbed fraction

m is the mass of the target region (kg)

k is proportionality constant (Gy-kg/MBq-s-MeV)

With S value formula:

$$S = \frac{k\sum_i n_i\,E_i\,\phi_i}{m} \qquad \text{(Eq. 2.8)}$$

Then, MIRD has simplified the equation into:

$$D = \tilde{A}.S \qquad \text{(Eq. 2.9)}$$

where:

Ã is the cumulated activity in source organ

S is S value derived from Monte Carlo simulation and selected phantom

The absorbed fraction ϕ, is defined as the fraction of the radiation energy absorbed in a target organ per radiation energy emitted by the source organ. Thus, the absorb fraction value is in between $0.0 \leq \phi \leq 1.0$. Nevertheless, according to the Monte

Carlo method, for the source organ that has a concentration larger than the average body concentration relies on the source and the target geometry. Meanwhile, by theory, the absorbed dose depends on the activity fraction that had been administered in the organ and on the organ rate of elimination.

2.4.1(b) Equivalent dose (H_T)

The equivalent dose is defined as the absorbed dose and the radiation weighting factor, W_R, which is used to reflect the biological effect. Furthermore, the equivalent dose depends on the LET of the different types of radiation. The equivalent dose usually used in radiological protection is suitable to be used for human estimation only. The S.I unit for equivalent dose is Sievert (Sv). Where 1 Sv is equivalent to 100 rem. Equation 3.0 defines the equivalent dose in mathematical term.

$$H_T = D.W_R \qquad \text{(Eq. 3.0)}$$

Where,

H_T is equivalent dose

D is the absorbed dose

W_R is the radiation weighting factor

2.4.1(c) Effective dose (ED)

The effective dose is defined as the product of equivalent dose weighted, H_T and tissue weighting factor, W_T. The tissue weighting factors of the effective dose represent the harmlessness of the tissue. In contrast, the equivalent dose weighted for an organ or tissues is the proportion between the stochastic effect's risk and the total stochastic