# Internal Dosimetry in Patients Undergoing a $^{177}$Lu-[DOTA0, Tyr3] Octreotate Therapy

**Thokozani Dudley Mkhize**

**24818852**

Dissertation submitted in fulfillment of the requirements for the degree Master of Science in Applied Radiation Science and Technology at the Mafikeng Campus of the North-West University

Supervisor: Prof. Manny Mathuthu

Co-Supervisors: Prof. Dr. Jan Rijn Zeevaart

Assistant Supervisor: Dr. Laurence Beels

November 2016

**DECLARATION**

I Thokozani Dudley Mkhize declare that this dissertation is of my own work. It is submitted for the degree of Master of Science in Applied Radiation Science and Technology at the North-West University, Mafikeng Campus. And to my knowledge it has not been submitted before for any degree or examination in any other University.

**Thokozani Dudley Mkhize** **Date: 20 March 2016**

**Candidate Name**

Signature

**Prof M. Mathuthu** **Date 25 March 2016**

**Supervisor**

**Prof J.R Zeevaart** **Date: 24 March 2016**

**Co-Supervisor**

**Dr. Laurence Beels**

**Assistant-Supervisor**

**ACKNOWLEDGEMENTS**

This work is dedicated to my late father Lamla Dalton Mkhize and my mother Lizzie Mkhize.

I would also like to acknowledge the following;

- To the Pule family in Mmabatho unit 14 for opening their home to me, words will never amount to what you did for me and my family. Ka leboga obuti Moreri.
- The North West University and CARST for giving the opportunity to come and pursue a qualification in Applied Radiation Science and Technology.
- The NRF for the funds to be able to study this M. Sc.
- To my supervisors, Prof. Mathuthu your encouragement and the advice you gave and for also trusting me with collecting data away from your supervision will always be appreciated and cherished.
- To Prof. Zeevaart I never imagined the doors you opened for me, may you keep opening doors for others who may follow. I hope I did you proud.
- To Dr. Beels, the work we did with my limited resource and helping me through this research is an experience that will help me as a Medical Physicist, may we continue and do greater things.
- To Dr. Modiselle and Mrs. Linda Nonjola, I am forever grateful for always availing yourselves to tend to my work and help me whenever I called upon you.
- To Dr. Thomas Ebenhan, you shared your office with me and taught me a lot about writing and carrying out a research, I thank you.
- To my siblings Gugulethu and Lulama Mkhize, your support has kept me going until now.
- To Dr. Mthokozisi Mkhize, without you I don't know where I would be. Because of you I am here, Khize Khabazela.
- To the Mkhize, Moshapalo, Thipe, Pule and Mthembu families thank you.
- To my partner, for letting me tour the country in pursuit of my dreams and still support me I thank you.
- I want to thank the National Research Foundation (NRF) of South Africa for supporting my study during my Honours degree which encouraged and enabled me to continue to this Masters degree.

*Khize, Khabazela kaMavovo.*

**ABSTRACT**

Patients with inoperable neuro-endocrine tumours (NETs) often have symptoms (i.e. diarrhea...) that decrease their quality of life. Targeted radionuclide therapy (TRT) can be used to increase the quality of life for these patients by relieving symptoms and suppressing tumour growth. For NETs, $^{177}$Lu-[DOTA-TATE] (a radiolabelled somatostatin analogue) is used as TRT. The organs at risk for this TRT are the kidneys and bone marrow, therefore, dosimetry should be performed in these patients to avoid side effects of over exposure (<25 Gy for Kidneys and 2 Gy for bone marrow). The aim of the study was to acquire dose measurements for the Kidneys using Mathematica 8™ for residence times and OLINDA/EXM™ for absorbed dose. Three patients with varying cycles of therapy were selected. The absorbed dose to the kidneys and to the tumour was calculated. For this, whole body images were acquired (GE Infinia Hawkeye 1) at 2hrs, 3hrs, 5hrs and 23hrs post injection of the therapeuticum. Regions of interest (ROI) were drawn over the kidneys and the tumour (liver lesions). The area under the curve of %Injected Activity vs. Time for all time points for each organ was used to calculate the residence times according to the MIRD dosimetry scheme using Mathematica 8™. These residence times were inputted into the OLINDA/EXM™ dosimetry software which then calculated equivalent radiation dose which can be converted to absorbed dose by multiplying it with injected activity. The results showed doses of about 0.36 Gy, 1.6 Gy and 0.75 Gy for kidneys on respective cycles, 1.34 Gy, 0.78 Gy and 0.696 Gy for the respective tumour in the liver. Results indicate how dose limiting organs, and tumour sites can be evaluated using the Mathematica 8™ and OLINDA/EXM™. Planar conjugate imaging can be used for dosimetry. From the work that was done during this research, an individualized patient dosimetry system was setup at another hospital, which provides another novel technique that supports physicists to learn and hopefully be able to improve on this novel technique for enhanced patient treatment and importantly for the safety of all who work with these radionuclides.

**List of Abbreviations**

| | |
|---|---|
| **2D** | - 2 Dimensional |
| **3D** | - 3 Dimensional |
| **DNA** | - Deoxyribose Nucleic Acid |
| **GEP** | - Gastro Entero Pancreatic |
| **keV** | - Kilo Electron Volt |
| **MeV** | - Mega Electron Volt |
| **MIRD** | - Medical Internal Radiation Dose |
| **NETs** | - Neuro-Endocrine Tumours |
| **OLINDA** | - Organ Level Internal Dose Assessment |
| **PET/CT** | - Positron Emission Tomography/Computed Tomography |
| **PRRT** | - Peptide Receptor Radionuclide Therapy |
| **RBE** | - Relative Biological Effect |
| **ROI** | - Region of Interest |
| **SPECT/CT** | - Single-Photon Emission Computed Tomography/Computed Tomography |
| **SSTA** | - Somatostatin Analogues |
| **TRT** | - Targeted Radionuclide Therapy |
| **β-emitter** | - Beta Emitter |
| **γ-rays** | - Gamma Rays |

## List of Figures



## List of Tables



## List of Images

# Table of Contents

# CHAPTER 1: INTRODUCTION AND PROBLEM STATEMENT

## 1.1 Introduction

A large number of patients suffering from cancer are successfully being treated due to an improvement in old therapy techniques such as surgery, external beam radiotherapy, chemotherapy and biotherapy. But still, therapy fails in about a third of patients treated. This can be due to the extent of the cancer spreading to multiple sites/parts of the body, which gave rise to new therapy modalities being developed, e.g. Targeted Radionuclide Therapy (TRT), usually focusing on the treatment of distant metastases. The use of ionizing radiation has emerged as the most commonly used treatment method for therapy; e.g. external beam radiotherapy, brachytherapy and radionuclide therapy [1].

In all of the above mentioned techniques, determination of absorbed dose is of importance not only in the tumour tissue but also in the surrounding tissue/organs in the vicinity of the target tissue/organ (Organs at Risk). This allows for one to be able to measure/estimate the therapeutic outcome and also to avoid complications from over treating/radiation overdose. The more accurately the absorbed dose is estimated, then more dose can be delivered to the tumor while staying within the safety range of the risk organs. In order to achieve a successful treatment, it is important to optimize the gap between absorbed dose to the tumour and exposure to the risk organs (Therapeutic window) [1].

The dose limiting organs when radionuclide therapy is the treatment of choice are the kidneys and the bone marrow. Usually in radionuclide therapy, a standard amount of activity (Lu-177 therapy 7400 MBq ) is normally used for all the patients as the standard). However, the injected dose deviates from 7400MBq due to the success of the radiopharmaceutical preparation techniques used with this therapy. In the form of prescription, the dose to organs varies considerably for each individual patient, which gives rise to gross absorbed activity differences in organs at risk and target tissue which may cause an over exposure of dosage to patients. Hence, the administered activity has to be given with an unnecessarily large safety margin. With this in mind, most patients may be undertreated or even over treated since each individual will have their own therapeutic window, which is not fully utilized (This reduces the chances of optimal palliative treatment being achieved). Although individual dosimetry is to be preferred, its accuracy is still low compared to e.g. external beam radiation therapy. The total number of decays in each organ or structure needs to be measured but since they are distributed over a long period,

e.g. 2-3 weeks for lutetium-177 ($^{177}$Lu), repeated measurements are needed. This is demanding both for the patient and for the logistics at a nuclear medicine department combined with the needed staff availability [1].

Currently, there are a few modalities used against different forms of cancers experienced. When targeted internal radionuclide therapies are used, the main aim is to deliver the highest possible dose to the target organ/tumor whilst also trying to spare dose to normal tissue/organ. To be able to track progress of the benefits and risks of therapy to individuals, patient-specific dosimetry is an essential requirement. There are various methods to estimate internal dose. Dose estimations could be based on either 2 dimensional (2D) planar gamma camera imaging or 3 dimensional (3D) imaging using Single-Photon Emission Tomography/Computed Tomography (SPECT/CT) or Positron Emission Tomography/Computed Tomography (PET/CT). Dosimetry is a guide for therapy optimisation when a suitable radionuclide and peptide has been selected. The Medical Internal Radiation Dose (MIRD) scheme [2] provides a more conventional method for calculating absorbed doses of radionuclides in internal organs. The optimal dose estimation includes pharmacokinetic, bio-distribution as well as washout information using the same radionuclide used for therapy which may be difficult owing to practical and physical reasons [3]. When treatment fails, it can often be attributed to a low response of the tumor to the therapy. To address this problem, new therapeutic treatments are being developed, among them targeted radionuclide therapy. Small peptides binding to Somatostatin receptors (Octreotide and Octreotate) can be labelled (bonded) with radioactive metal ions and used for both receptor imaging and radiation therapy [3].

Peptide Receptor Radionuclide Therapy (PRRT) radio-labelled with Somatostatin Analogs (SSTA) is now established as a treatment modality in Gastro Neuro-Endocrine Tumours (NETs) and therefore one of the most frequently used targeted radiotherapies [4]. NETs originate from the Neuro-Endocrine cell system, which is largely distributed in the body, and it is a heterogeneous group of neoplasms characterized by embryological, biological and histo-pathological differences. The sites that mostly have these endocrine cells are the gastro intestinal tract (70%) and the bronco-pulmonary system (25%), followed by the skin, the adrenal glands, the thyroid and the genital tract. Present classification is based on tumor biology and patho-histological features (cellular grading, primary tumour size and site, cell proliferation markers, local or vascular invasiveness and the production of biologically active substances) [5].

In evaluating absorbed dose to the kidneys, renal damage is believed to be reduced during the therapy. The radionuclide $^{177}$Lu labelled to [DOTA0, Tyr3] Octreotate (DOTATATE) is used for in vivo therapy (Cubital vein) of NETs. Because of its nuclear decay characteristics and chemical properties, the $^{177}$Lu isotope has shown some effect on the renal function toxicity due to its main flushing route through urine, but in comparison to other available radionuclide's, such as the $^{90}$Y isotope, it is considered to be a radionuclide which is better tolerated by the kidneys. The determination of radionuclide uptake by the tumor labelled with the peptide Octreotate and absorbed dose to the organs at risk requires knowledge of patient specific time varied bio-distribution of the activity in the body. In order to obtain accurate dosimetry calculations, the individual kidney volumes, dose rate, blood serum (for bone marrow dose) and fractionation all play an important role. This enables the prediction of risk for renal function difficulties and bone marrow overexposure. Doses are based on the volume and the average activity uptake values over the Region of Interest (ROI) (In cases where bone marrow dosimetry is also measured the blood volume activity will be required), using the planar imaging conjugate view method. From the measured data we calculated the %FIA and plotted this against time. This gave a time activity curve which was then integrated by fitting a bi-exponential curve. Then the area under this curve was our residence time. The value of this residence time (integrated area under the activity curve) is then used as an input to the OLINDA Software for dosimetry calculation. The Organ Level Internal Dose Assessment, [OLINDA] dosimetry computer code thus gives the organ dose estimations and the dose distributions. For this purpose, the gamma camera for whole body imaging, SPECT and CT was used [6].

The characteristics of the $^{177}$Lu radionuclide used are: it is a medium energy β-emitter with a maximum energy of 0.5 MeV and a maximum tissue penetration of around 2 mm. It has a half-life of about 6.65 days. $^{177}$Lu also emits low-energy γ-rays at 208 KeV and 113 KeV with 10% and 6% abundance, respectively. The shorter β-range of $^{177}$Lu provides better irradiation of small tumours, in contrast to the longer β-range of $^{90}$Y which allows more uniform irradiation in large tumours that may show heterogeneous uptake. With the use of low-energy γ-rays at 208 KeV and 113 KeV emitted by $^{177}$Lu, accompanied with the therapeutic β-radiation, not only can post treatment scans be acquired, but patient dosimetry can also be performed. It has been argued by some that the window optimization for gamma acquisition should be set to the highest gamma, 208 KeV as it has less scatter and may improve image acquisition. However the absorbed radiation doses to dose-limiting organs such as the kidneys and bone marrow can be calculated to make it possible in future to model dose to an individual patient. The absorbed radiation dose to

the kidneys has been shown to vary widely between patients treated with $^{177}$Lu-[DOTA0, Tyr3] Octreotate [7]. The knowledge of the mean absorbed dose to the dose limiting organs is of the utmost importance. Also knowing the patient specific optimum treatment cycle would be of value for a patient based internal dosimetry treatment plan.

## 1.2 Background

### 1.2.1 Ionising Radiation

Ionising radiation is radiation that carries enough energy to eject orbital electrons from an atom or molecule, thereby "ionising" (removing) an orbital electron. Ionising Radiation is composed of energetic subatomic particles (alpha particles, beta particle and neutrons), ions/atoms and electromagnetic waves on the high-energy end of the electromagnetic spectrum [8].

#### *1.2.1.1 Directly Ionising Radiation*

This type of radiation removes orbital electrons from the atom directly when they interact with matter (alpha and beta particles) and represents charged particles.

**Alpha Particles**

The alpha (α)-particles are helium nuclei comprising of 2 protons and 2 neutrons ($^4$He), they are highly ionising particles due their heavy composition (which equates to more DNA damage than all other Ionising radiation when localised to a tumor site). Although they have low penetration (they can be stopped in a few centimeters in air or human skin), when inside the body they are highly effective to localized areas [8].

**Beta Particles**

Beta (β) - particles are high energy particles, which may be either positive or negative. They are emitted by a radioactive nucleus. The beta electrons are used for therapy whilst the beta positrons may be used for imaging PET/CT scans [8].

**Gamma Radiation**

ɤ-rays are photon radiations which are produced by nuclear reactions, subatomic particle decay or radioactive decays within a nucleus. Photons are called X-rays (they have lower energy than gammas) when they are produced outside of the nucleus of an atom by x-ray tubes (when an accelerated electron decelerated within the nucleus of an tungsten) [8].

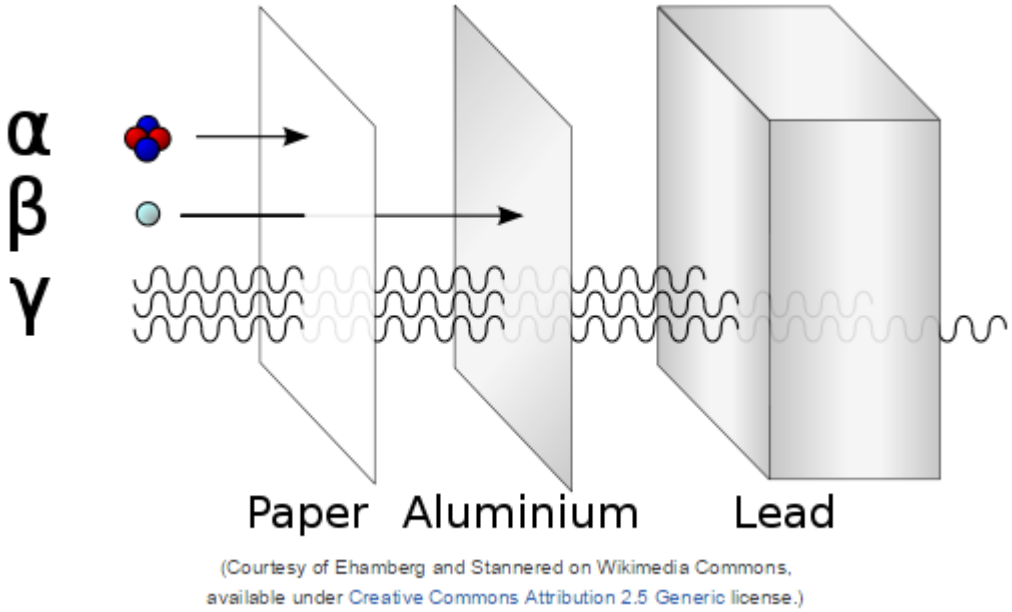



**Figure 1:** Different types of radiation and their interactions with matter [8]

#### *1.2.1.2 Indirectly Ionising Radiation*

Indirectly ionising radiations are electrically neutral radiations which do not interact strongly with matter (e.g. neutron radiation) [8].These interactions are some that help in contributing towards the understanding and, utilization of radiation in medicine and also to track the effects of radiation on living cells.

### 1.2.2 Targeted Radiotherapy

To be able to calculate dose distribution, advanced calculations such as Monte Carlo simulations are required in order to get reliable results. Administration of radionuclides according to body weight or surface is insufficient to individualize dose to be administered because the kinetic variations between individuals may be large and unpredictable. Dose planning by determining the individual kinetics before therapy begins, improves the ability to predict the outcome though it may probably not be sufficient because of possible changes in the tumor mass and in organ function that may occur during TRT (Reference). An accurate calculation of the absorbed dose is then best performed by following the actual uptake of the radionuclide in tumours and critical organs during therapy which in our instance follows the image projections from the gamma camera [1].

### 1.2.3 Dosimetry

The absorbed dose of radiation is defined as the amount of energy that is deposited by ionizing radiation in tissue of a given mass, with units of J/kg or Gray (Gy). In nuclear medicine dosimetry, charged particles (alpha and beta particles) are usually assumed to be locally absorbed since their ranges are less than the spatial resolution of the nuclear medical detector (Reference). One exception may be high-energy beta radiation. Gamma radiation above 70 KeV is locally absorbed to a low degree and yields a substantial crossfire (This occurs when a source organ accumulates an amount of dose from a radionuclide and in turn irradiates organs/tissues close/surrounding the source organ) of adjacent organs (Reference). The bulk of the emitted gamma energy exits the body which justifies gamma imaging. Radiation causes damage by depositing energy that affects the DNA. Single strand breaks can be repaired more efficiently than double strand breaks. Depending on radiation type, absorbed dose and absorbed dose rate, these damages can be predicted. In external beam radiotherapy, radiation is usually administered by daily fractions with a high dose rate during several weeks. In radionuclide therapy the radiation is delivered continuously with a low dose rate that also will decrease during therapy due to half-life and activity elimination. The biological effect from different administration routes may vary considerably and organ dose limit obtained in external beam therapy has to be applied with care in radionuclide therapy (Reference). Moreover, the radiation dose in external beam therapy is delivered stochastically exclusively whereas in radionuclide therapy the local radionuclide concentration as well as the cellular and intracellular distribution may affect the absorbed dose to the cellular DNA. This is particularly true when low energy electrons such as Auger electrons are emitted in the radionuclide decay. If such radionuclides are included into the DNA molecule itself, the Relative Biological Effect (RBE) may increase substantially [1] [3].

## 1.3 Problem Statement

Patients with inoperable neuro-endocrine tumours often have symptoms (such as diarrhea, flushing, etc.) that decrease their quality of life. Radiolabelled somatostatin analogues can be used as a therapy (e.g. $^{177}$Lu-[DOTA0, Tyr3] Octreotate Therapy) to relieve symptoms and suppress tumor growth. A critical organ for therapy is the kidney. Therefore, dosimetry should be performed in patients undergoing treatment with $^{177}$Lu-[DOTA0, Tyr3] Octreotate therapy, to avoid side effects such as kidney (over) exposure. Doing dosimetry on the early stage uptake (less than 30 hours post injection) can help to ascertain whether the treatment over time meets the dose limits for non-target organs and can contribute in determining minimum scan time to have a basic

early stage dosimetry when administering such a treatments. This study will evaluate internal dosimetry in patients undergoing a $^{177}$Lu-[DOTA0, Tyr3] Octreotate therapy.

### 1.4 Aim and Objectives

#### 1.4.1 Aim

This research aim was to acquire dose measurements for the Kidneys using Mathematica 8™ for residence times and OLINDA/EXM™ for absorbed dose in order to accurately calculate the radiation dose to the kidney and target organ making use of existing data.

By performing dosimetry in patients undergoing a $^{177}$Lu-[DOTA0, Tyr3] Octreotate therapy, dose (in terms of radiation) to the kidneys can be monitored. Administered activity (injected dose) per cycle can be adapted for individual patients to allow for an optimally absorbed dose to the tumor and to assure a safe cumulative renal absorbed dose.. This will pave the way for future patient optimization studies prior to treatment.

#### 1.4.2 Objectives

The objectives of our study were:

- to get acquainted with the MIRD schema and usage of OLINDA/EXM™.
- To calculate organ dose for some patients undergoing PRRT with $^{177}$Lu-DOTATE.
- To use Organ Level Internal Dose Assessment (OLINDA)/EXM™ (Exponential Modeling) in assessing dose uptake and clearance from the liver and the kidneys.
- To determine organ dose using OLINDA/EXM™ for medical internal radiation dose (MIRD) to the liver and the kidneys.

### 1.5 Significance of Study

In performing patient based internal dosimetry, treatment of Neuro-Endocrine Tumours can be optimized without damaging healthy tissue, this will benefit the individual patient, whilst meeting radiation protection guidelines (dose limits). In this study, internal dosimetry in patients undergoing a $^{177}$Lu-[DOTA0, Tyr3] Octreotate was performed concentrating on the early stage uptake dosimetry of the therapy (scans not more than 30 hours for a single cycle on 3 patients). The late stage clearance of the therapy requires late stage scans which were not done in this study. This was due to logistical problems from the patient's side. Internal radionuclide radiation dosimetry specifically deals with the accounting of radiation energy deposited in tissues due to a radionuclide within the body.

# CHAPTER 2: LITERATURE REVIEW

## 2.1 Introduction

The main objective of targeted radionuclide therapy (TRT) is to selectively deliver radiation to cancer cells and/or diseased tissue with minimal toxicity to surrounding normal tissues. For a successful radionuclide therapy, an individualized therapy approach is needed to integrate diagnostic testing for presence of a molecular target for which a specific treatment/drug is optimized (Fig. 2). Individualized therapy is a new form of therapy approach that helps to improve therapy selection on the basis of specific molecular features of disease, increased probability to predict side effects due to improved patient-specific absorbed dose estimates, and new ways to objectively monitor therapy response. Currently, radionuclide therapy remains an important treatment option because ionising radiation from radionuclides can irradiate specific targeted cells and inhibit growth in the benign and cancerous lesions that result from proliferative diseases. Radiation inhibits the reproduction of cells (By fractionating the therapy, we can give normal cells enough time to recover whilst targeting cancerous cells), this occurs when cells are damaged via DNA in the cell nucleus. It has also been recommended that by combining the therapy with other treatment modalities (i.e chemotherapy cocktail), this may have a benefit to the patients [9].

From the literature published, the reason why the kidneys are the dose limiting organs is stated as because it is the primary source of excretion of the remaining radionuclide activity. This is why the amino acids administered help in making the body (urine) flush out quickly. Octreotate is a combination of the linker of Lu-177 and the peptide (-tate).

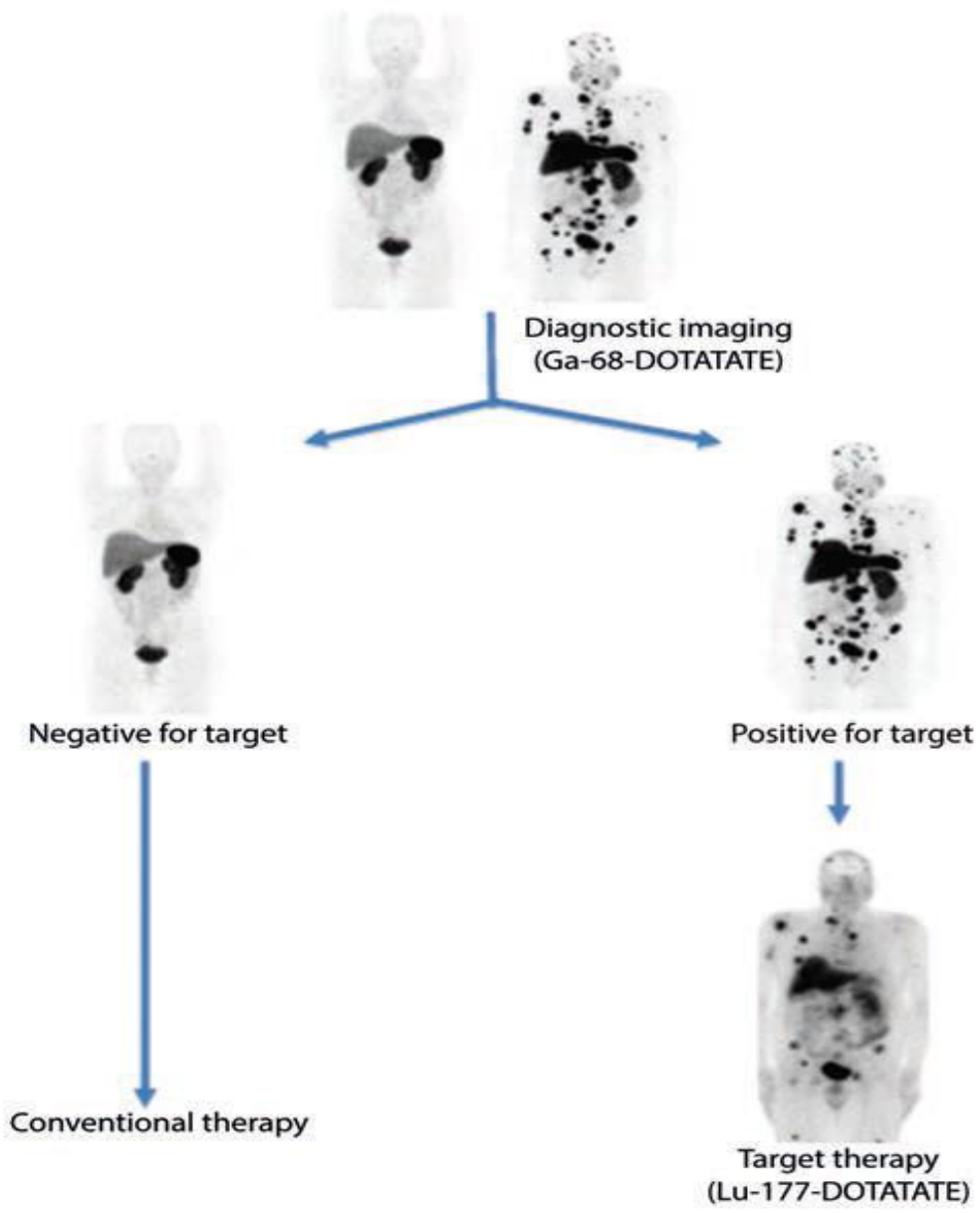



**Figure 2:** Imaging process for the detection of metastasis with Ga-68 Octreotate PET/CT and the selection of which action to take from the diagnostic images [9].

### 2.2 Peptide Receptor Radionuclide Therapy: Neuroendocrine cancer

Peptide Receptor Radionuclide Therapy (PRRT) is a treatment modality where a radionuclide is bound to a peptide that is specific to a site in the body (e.g. a Somatostatin Analogue Fig. 3). In PRRT, a receptor ligand is bound to a radioactive isotope (normally $^{177}$Lu or $^{90}$Y). Commonly used radiopharmaceuticals are $^{177}$Lu-[DOTA0, Tyr3] Octreotate and $^{90}$Y-[DOTA0, Tyr3] Octreotate. PRRT is the treatment of choice in adult patients with Neuro-Endocrine cancers which are inoperable who have residual disease following surgery or other minimal invasive therapy, or

who have metastases. PRRT relies on the knowledge that about 70% of Neuro-Endocrine tumours express somatostatin receptors (especially subtype 2) on the cell surface, which presents an excellent target for therapy. The radionuclide is thereby bound to the tumor cells by these Somatostatin analogues, which decay, with the resulting radiation damaging surrounding cells. Positive Somatostatin receptor scintigraphy with $^{111}$In- or $^{99m}$Tc-Octreotide or with Positron Emission Tomography/Computed Tomography (PET/CT) using $^{68}$Ga-[DOTA0,Tyr3] Octreotate is an important tool for predicting the efficacy of PRRT, and for the assessment of the response to PRRT (Fig. 2). In the case of poorly differentiated tumours, PRRT is less effective. Accumulated evidence from clinical data indicates that partial and complete responses may be achieved in almost 50% of patients who undergo this kind of therapy, and that the duration of the therapy response is more than 3 years The patients' quality of life also improves significantly after treatment with $^{177}$Lu-[DOTA0, Tyr3] Octreotate. Compared with other modalities for such tumours, patients treated with $^{177}$Lu-[DOTA0, Tyr3] Octreotate show an increase in overall survival of several years from the time of diagnosis and side-effects of PRRT are typically seen in the kidneys [10].

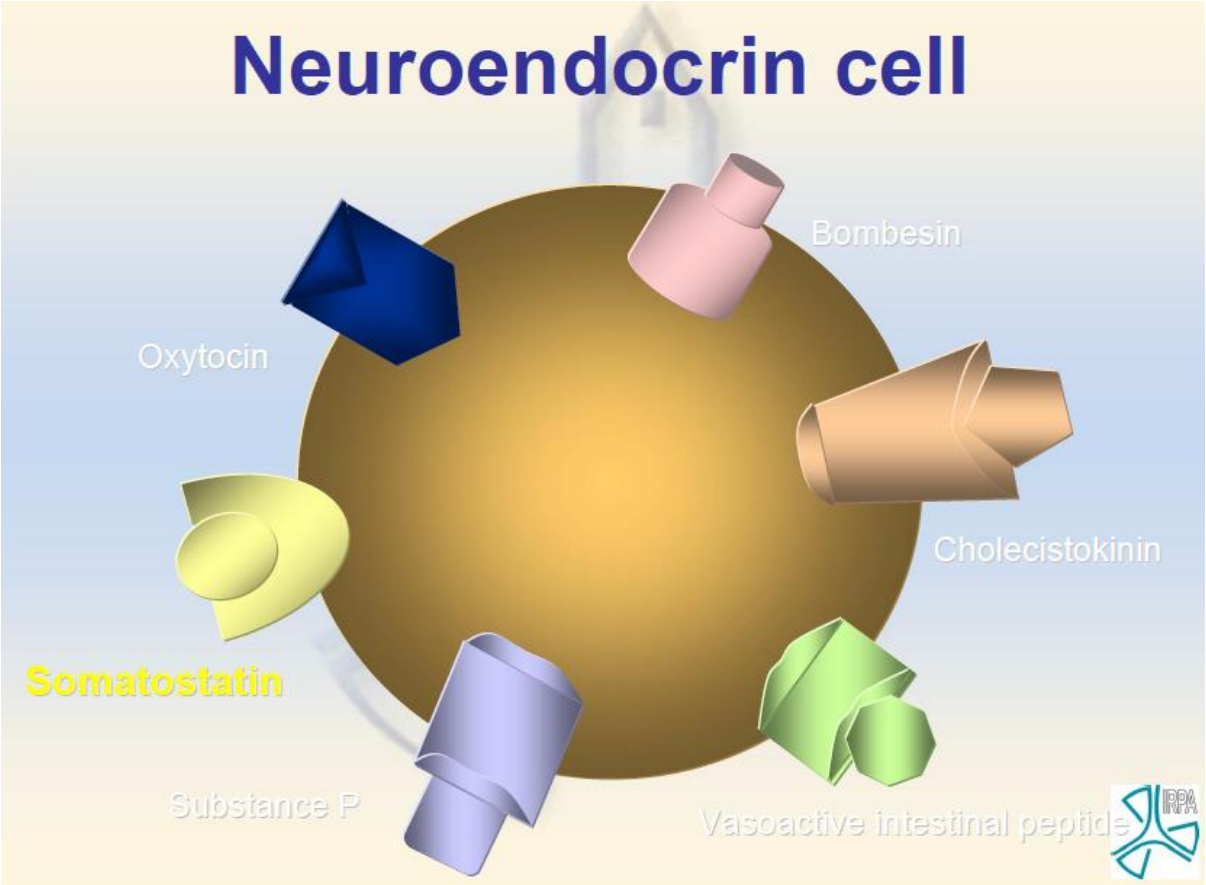



**Figure 3:** Neuroendocrine cell and some of the ligands it has receptors for [10]

### 2.3 Patient Dosimetry methods

Garkavli et al., (2009) used three different quantification methods to evaluate the absorbed dose to the kidneys. The first method involved common planar activity imaging, from which the absorbed dose was calculated using the MIRD formalism from CT scan-based kidney images. For this method, two regions of interest (ROIs) locations for the background correction were investigated. The second method also included single-photon emission computed tomography (SPECT) data, which were used to scale the amplitude of the time-activity curve obtained from planar images. The absorbed dose was calculated in the planar method. The third method used quantitative SPECT images converted to absorbed dose rate images, where the median absorbed dose rate in the kidneys was calculated in a volume of interest defined over the renal region [11].

Zanzonico and Chaitanya (2008) used an algorithm which was clinically practical for the treatment of liver cancer by administering rhenium-188 ($^{188}$Re)-labeled lipiodol delivered through the hepatic artery. This algorithm was based on the maximum tolerated-activity paradigm for radionuclide therapy. A small amount of diagnostic activity of 188Re-labeled lipoid was administered to the patient before the actual radionuclide administration. At approximately 3 hours after administration, the activities in the normal liver, liver tumours, lungs, and total body were measured by gamma camera imaging using the conjugate-view method, with first-order corrections for attenuation (using a 188Re transmission scan) and scatter (using the "dual-window" method) [12].

Sandstrom (2011) looked at the ability to measure radioactivity distribution of radionuclides in therapy. SPECT measurements of $^{177}$Lu showed good spatial resolution and reasonable quantitative accuracy. A new method to calculate absorbed dose to solid risk organs and tumours was developed and applied. This included kinetic data which was obtained by repeating SPECT measurements. Radiation concentration was determined in small volumes of interest, which could then be multiplied by a constant to obtain the absorbed dose because it was shown that cross-fire, a situation where the target organ irradiates nearby organs, was negligible in organs with high activity concentration namely the kidneys. The SPECT dosimetry method showed that when compared to other methods, it gave better results with less effort [1].

Baka, Ploussi et al., (2014) based their individualized patient dosimetry calculations on planar and SPECT images. ROIs were drawn and counts determined around the tumor and surrounding

tissue (for background correction), this was done for the liver, kidneys and spleen. In planar technique, the ROIs were drawn in both anterior and posterior images while SPECT counts were measured per slice. For count conversion to activities, calibration factors to convert pixel counts to activity in an organ were calculated. Planar and SPECT images of cylindrical water – filled phantom, with five different known amounts of activity, were obtained. Corrections for scatter attenuation, collimator efficiency and detector response were calculated. Absorbed doses were calculated using MIRD formalism and S values of organs were calculated using the RADAR system. The absorbed doses to an organ per unity administered activity were comparable for both planar and SPECT techniques [13].

Sandstrom, et al., (2012) again used planar whole-body and SPECT/CT images of the abdomen acquired at 24, 96, and 168 hrs post injection. Calculation of the absorbed radiation dose to the bone marrow was based on blood and urinary activity curves combined with organ based analysis of the whole-body images. The absorbed dose to the kidneys was calculated from the pharmacokinetic data obtained from SPECT/CT [3].

Guerriero, et al., (2013) Studied kidney dosimetry in $^{177}$Lu and $^{90}$Y. They investigated the most adequate timing for imaging and time-activity interpolating curve, as well as the performance of a simplified dosimetry, by means of just 1 or 2 scans. Also the influence of risk factors and of the peptides (DOTATOC versus DOTATATE) was considered. A total of twenty eight (28) patients treated at first cycle with $^{177}$Lu DOTATATE and 30 with $^{177}$Lu DOTATOC underwent SPECT scans at 2, 6, 24, 42, and 64 hrs after the radiopharmaceutical injection. Dose was calculated using trapezoids, mono-exponential, and bi-exponential functions [10].

Amato, et al., (2011) mentioned that a dosimetric protocol consists of the acquisition of multiple planar whole-body (WB) scans to obtain bio-kinetic data over time (at least 4-5 acquisitions at different times); complementary SPECT imaging to evaluate intra-organ activity distribution (especially at the level of the kidneys and in tumour lesion); WB transmission imaging for attenuation correction; as well as blood and urine samples. Anatomical CT imaging provides important parameters for organ mass evaluation. Dosimetry was performed using the MIRD formalism, in order to obtain average dose estimates at the organ level assuming standard phantom models, with possible organ mass adjustments according to patient data. The Voxel dosimetry method or direct Monte Carlo simulation can provide more reliable dose estimates [5].

Schuchardt, et al., (2013) stated that dose estimation requires an accurate determination of the time-dependent activity of the source regions. The most important feature is the correct evaluation of the distribution and the kinetics of the administered radiopharmaceutical. Dosimetry was performed according to the MIRD protocol and adapted to the special conditions called Bad Berka Dose Protocol (BBDP). The BBDP entailed conjugated planar whole-body scintigraphy at 0.5, 3, 24, 48 and 72 hrs post injection of the treatment being analysed by using ROIs with 'HERMES-WHOLEBODY DISPLAY$^{TM}$ and the time-dependent organ and tumour activities are determined with Microsoft Excel$^{TM}$. The cumulated activity was calculated using the software OriginPRO8.1G$^{TM}$ and a mono- or bi-exponential fit of the time-activity curves. Mean absorbed doses were finally estimated using the software OLINDA/EXM$^{TM}$ by inputting residence times [4].

**2.4 MIRD Schema**

The absorbed dose calculations are an integral part for evaluation of the risks involved in the application of radionuclides to medical studies, whether it is imaging, therapy, or non-invasive physiologic and metabolic studies. Although the calculation of absorbed dose can become rather complex when using Monte Carlo calculations, the most commonly encountered problems can be reduced to a few basic operations by using the MIRD system. For such calculations, the main inputs needed to complete the calculations are the biologic distribution data (pharmacokinetics), the physical properties of the radionuclide (physical and biological half-lives), and the method or scheme that combines the biological and physical data into the dose estimates. The calculation of absorbed dose to tissue can be considered as a conversion of activity into energy emitted, and then into energy absorbed/deposited per unit mass. The conversion involves a lot of factors but these can be lumped into a single number called the S value. The mean absorbed dose ($\overline{D}$) for a particular organ is then the product of the cumulated activity ($\tilde{A}$) and the appropriate S value:

$$\overline{D} = \tilde{A} * \mathrm{S}$$

The complete dose estimate for a target organ requires summation of the individual contributions from each source organ in addition to the contribution from the target organ itself [2].

**The MIRD Schema – Simplified Equations**

When one considers a radiopharmaceutical that emits only a single type of radiation located in one tissue, it is called the source organ or tissue. Seeking an expression for radiation absorbed by another tissue, the target organ or target, we have:

$$\overline{D}/A_0 = \text{ϒ}*\text{S}$$

Where $\overline{D}$ is the mean absorbed dose, $A_0$ is the administered activity, and ϒ is the residence time, an effective time that the administered activity spends in the source organ, S is the dose to target from unit cumulated activity in the source organ and is called *dose per unit cumulated activity* [2].

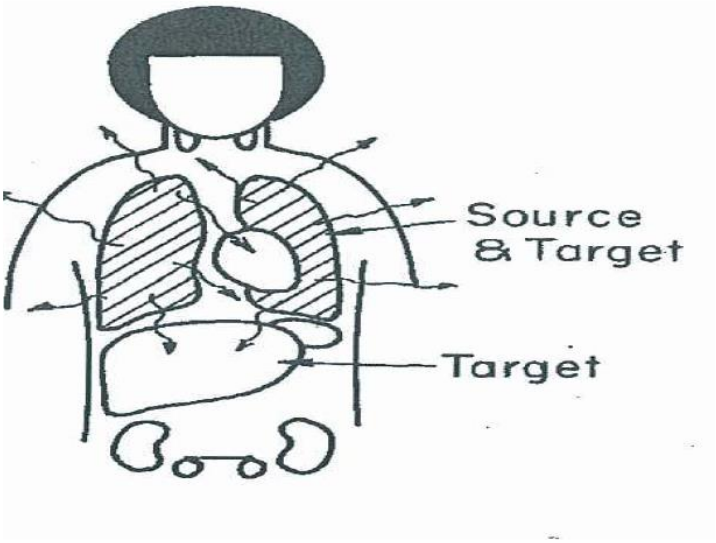



**Figure 4:** Source and target formalism [2]

In general, radiopharmaceuticals of major interest in nuclear medicine emit either photons or electrons. Since both possibilities need to be considered as a single formulation, they are named particles. And E will be the mean energy per particle, and n be the number of particles emitted per transition. If A is the activity in the source, then we can add up all transitions that take place during some time interval of interest and call it the *cumulated activity*, [2] then:

$$\overline{A} * \text{n}*\text{E}$$

The radiation will be emitted equally in all directions, since only some fraction it the radiation will be absorbed by the target (depending on the size, shape and distance from source). The fraction is given ∅ and named absorbed fraction. Then:

$$\overline{A} * n * E * \emptyset$$

This is the energy absorbed in (imparted to) the target during the time interval of interest. It then states that the mean absorbed dose to the target is:

$$\overline{D} = (\tilde{A} * n * E * \emptyset)/m$$

where *m* is the mass of the target organ [2].

The above equation is the basic equation for radiopharmaceutical dose calculations. From the equation, the mean energy emitted per nuclear transition is represented by the symbols:

$$\Delta = n * E$$

Then:

$$\overline{D} = (\tilde{A} * \Delta * \emptyset)/m$$

When this above equation is simplified, the *specific absorbed fraction* as the absorbed fraction per unit mass is:

$$\Phi = \emptyset/m$$

Which then gives:

$$\overline{D} = \tilde{A} * \Delta * \Phi$$

The symbol S will thus be

$$S = \Delta * \Phi$$

Then:

$$\overline{D} = \tilde{A} * S$$

This equation shows then that S is the mean absorbed dose in the target organ per unit cumulated activity in the source [2].

When the dose to the target is required, it would be convenient to express this in terms of *dose per unit administered activity*. When defining residence time in the source as:

$$\tau = \tilde{A}/A_0$$

$A_0$ is the administered activity. The mean dose to the target organ per unit administered activity is:

$$\overline{D}/A_0 = \tau * S$$

S values are put in an extensive table where they can be used, OLINDA uses the methodology from this MIRD schema. The method is divided into a) determining the residence time ($\tau$), which depends on radioactive decay and the physiologic behaviour of the radiopharmaceutical, and b) determining S, which is a physical quantity that depends on the nature of the radiations and their absorption characteristics, and on an anatomic model of a standard patient (this though can be adjusted in OLINDA when the organ can be observed as a bit larger than normal) [2].

These above equations are an introduction into calculations and algorithms used by OLINDA and its preceding RADAR to calculate internal dose [2].

### 2.5 Role of patient-specific dosimetry

The role of patient-specific dosimetry can be summed up by the following; it helps in the identification of critical organs (targeted and at risk), the side effects in normal tissue, the maximum administrable dose, it can also help in validating methods used to reduce absorbed dose to organs at risk and finally to quantify dose to the target organ.

### 2.6 Importance of Internal Dosimetry

The importance of internal dosimetry is that it gives a bio-distribution of the radionuclide in the body, which leads to dosimetry being performed. It also helps to correlate planned treatment to actual therapy.

## CHAPTER 3: METHODOLOGY

### 3.1 Target Group

Data from 3 patients undergoing $^{177}$Lu-[DOTA0, Tyr3] Octreotate therapy at the Steve Biko academic hospital which is in Tshwane South Africa, at the nuclear medicine department was gathered. No specific attribute was focused on.

### 3.2 Imaging Protocol

Scans acquired on a General Electric Infinia Hawkeye 1™ Gamma Camera

**Scan Protocol:**

8cm/min table speed

256x256 matrix

MEGP Collimator

Anterior/Posterior Acquisition

Dual energy window 113-208 keV (20 % width)

### 3.3 Data Collection

#### 3.3.1 Time Integrated Activity

Generally, the bio-kinetics of a radiopharmaceutical within the human body is influenced by the type of the carrier molecule (peptide); its physiological and pathological pathway; the route of administration and preparation; and the clinical state of the patient. In order to plan for a patient specific treatment, only an accurate individualized dosimetry can be used. In order to calculate the cumulated activity, the activity uptake in each organ or ROI must be properly sampled after administration. In principle, more measurements allow a more accurate fit of the A = A(t) curve, and consequently, a better estimation of the total number of disintegrations [5]. Repeated measurements are necessary to sample the kinetic behaviour of the radioactivity and to calculate the total number of decays in different structures. More frequent measurements give a more accurate determination of the time-integrated radioactivity, implying a more accurate determination of the dose integrals. At least four measurements in each phase of the kinetics were performed. $^{177}$Lu-[DOTA0, Tyr3] Octreotate is a small peptide and two phases can be identified in its kinetics: one with rapid clearance from blood (not considered in this study) and fast organ uptake that is completed 6-8 hrs after the administration, and a second slow elimination phase that can be represented by a single exponential function (not considered due to logistics of patients and gamma camera time). The cumulative activity was estimated with the exponential function

method [14], [15]. The simplest model applies when the uptake phase, i.e. the phase in which the radiopharmaceutical is accumulating in the organ and its radioactivity rises with time, is short enough to be considered instantaneous (about an hour or less). Consequently, immediately after administration, the washout phase begins [5]. An exponential fit was made to the measurement points obtained; the area under the curve was integrated using Mathematica 8 to get an estimate of cumulative activity which consequently gave residence times.

### 3.3.2 Patient-Specific Dosimetry

The body gets its radiation when a radionuclide is injected (In our case through the Cubital Vein), inhaled or exposed. In relation to radionuclides injected, organs in the body may receive the radiation directly from the radionuclide or from surrounding organs. The count rates were measured by manually drawn ROIs of the kidneys and organs with tumour. Background counts were measured close to the ROIs and a background subtraction method was performed. Planar conjugate images were acquired 30 minutes post radiopharmaceutical injection, at 1 hr, 2 hrs (only in one cycle of the patient therapy), 4 hrs and 24 hrs post injection. Activity was calculated for the tumour (liver tumours) area and kidneys. Curves of percent activity as a function of time were drawn for each organ. The area under each curve and time axis was the percentage cumulative activity. Cumulative activity (Ac) is measured in $MBq.hr^{-1}$ for each organ, and then we calculated residence time by dividing the percentage cumulative activity by the committed activity, before finally working out the residence time from the subsequent results. The MIRD (Medical Internal Radiation Dose) scheme calculates the mean absorbed dose using OLINDA/EXM™ from the residence times calculated, assuming an average tissue deposition of energy and a uniform distribution of the radiopharmaceutical. A Microsoft Excel™ calculation spreadsheet was developed so that the count rate was converted to activity [13].

### 3.3.4 Absorbed Dose

In the OLINDA/EXM™ input, the derived time-integrated activity concentrations had to be recalculated to cumulative radioactivity per organ. OLINDA/EXM™ provides a set of standard organ weights but true organ weights can also be entered into the calculations. The two kidneys are treated as one organ and individual kidney doses are not directly obtained. In therapy the effective dose is of less concern but the main interest is to calculate the absorbed dose in organs with high radioactivity concentrations, usually the kidney, the liver and the spleen. These solid

organs then act like strong radioactive sources irradiating adjacent organs (cross-fire effect), but since adjacent organs have lower radioactivity concentrations the cross-fire back is relatively small [13]. In this study, the dosimetry calculations were done using a spreadsheet (which had to be adapted for $^{177}$Lu-[DOTA0, Tyr3] Octreotate therapy) by T.D. Mkhize. Residence times for each measured organ to input in OLINDA/EXM™ were done using Mathematica 8™, a bi-exponential integral was acquired so that it could be normalised to the injected dose for the residence times.

### 3.3.5 Camera Sensitivity

A Petri dish of diameter 10 cm was filled with known activity mixed with saline and placed on top of one head of the Gamma camera, the following equation was used to calculate Sensitivity:

$$\textbf{Sensitivity} = (I_A * I_P)^{1/2} / A_j$$

**$I_A$ and $I_P$** are Anterior and Posterior background corrected ROI counts/second

### Activity in the Organ from Images

$$A_{ORGAN} = (I_A * I_P)^{1/2} / \text{Sensitivity}$$

**$A_{ORGAN}$** is the background corrected activity in the organ of interest

From the above equation, if we multiply $A_{ORGAN}$ by 100 and divide the quotient by the Injected Activity in the syringe, we get a percent Injected activity (%IA), that could be calculated and a %IA-Time graph plotted. Then the residence time is calculated from the area underneath the curve. (**NB:** The residence time will be in units of percent per hour, diving by 100% will give us the correct units of residence time [$hr^{-1}$]).

## CHAPTER 4: RESULTS

The $^{177}$Lu-[DOTA0, Tyr3] Octreotate administrations were well-tolerated without any serious side effects. Three patients were observed and their absorbed dose for a single cycle calculated using the MIRD scheme with the OLINDA/EXM™ program. Off the three patients, for each patient a cycle was calculated (cycle 1 for 1$^{st}$ patient, cycle 2 for the 2$^{nd}$ and finally cycle 3 for the 3$^{rd}$ patient), there was no particular reasoning in the selection of patients or the cycles but for the research to be successful 4 time points were needed and those were the points for the available patients. Figure 5 shows the kidney dosage curve for the patients and clearly shows the difference of each patient's clearance rate for the therapy, this again shows the importance of individualized patient dosimetry. Figure 6 shows the curves for the liver (Tumor areas) and again as can be seen from the early uptake curves, individualized patient dosimetry show how each individual is unique and must be treated as such when it comes to dosimetry.

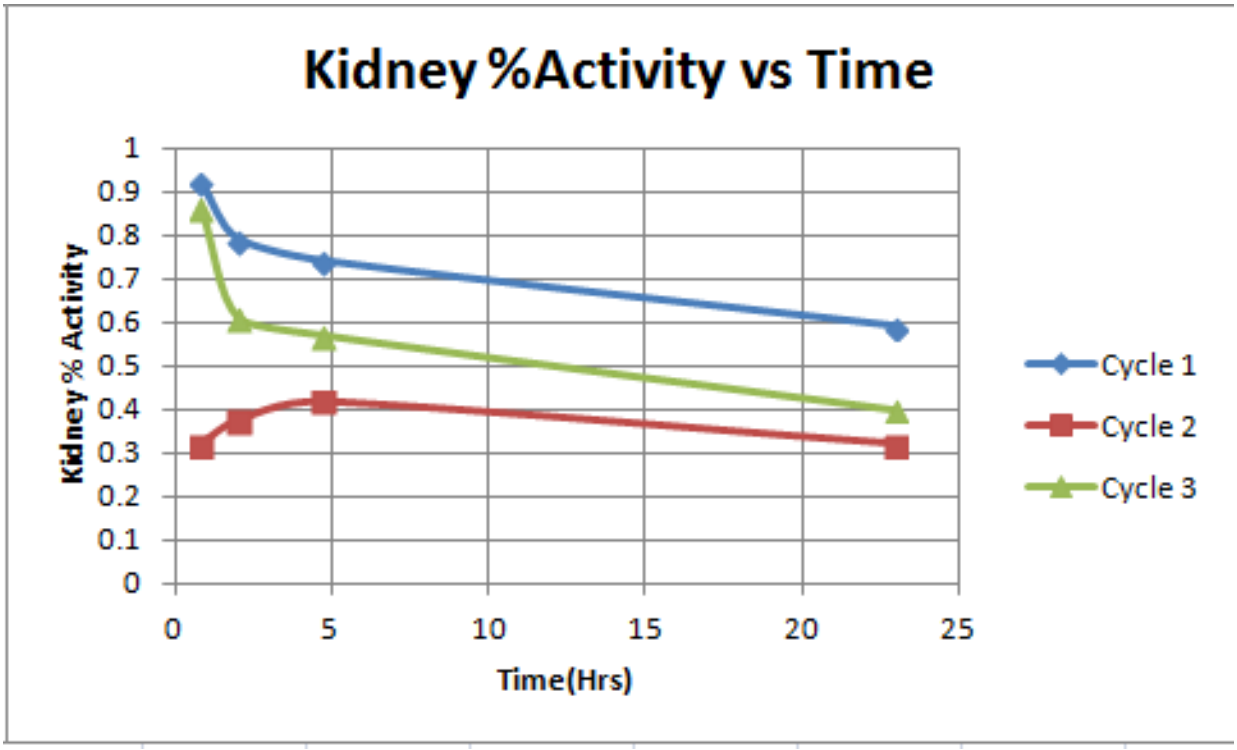



**Figure 5:** Kidneys clearance Percent Activity vs. Time curves

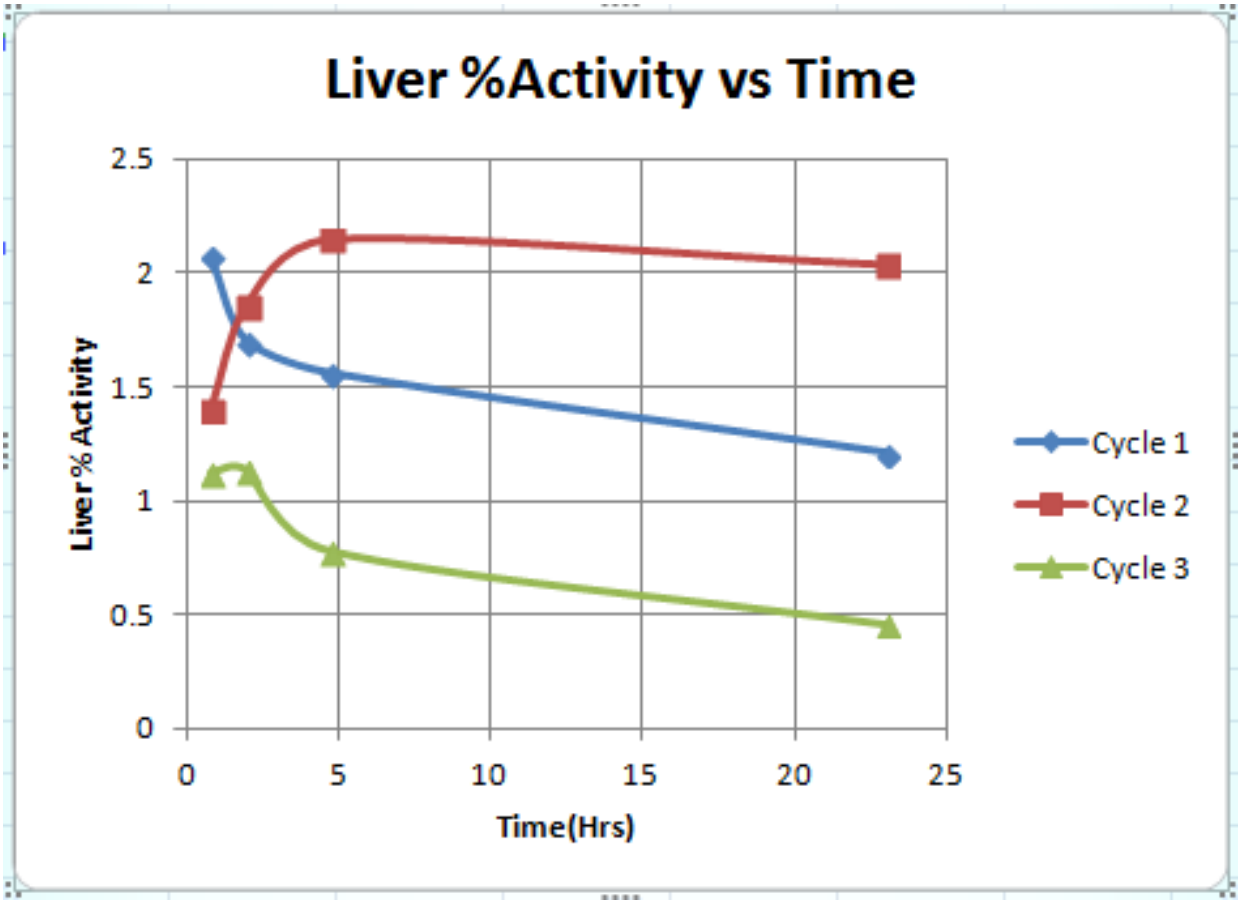
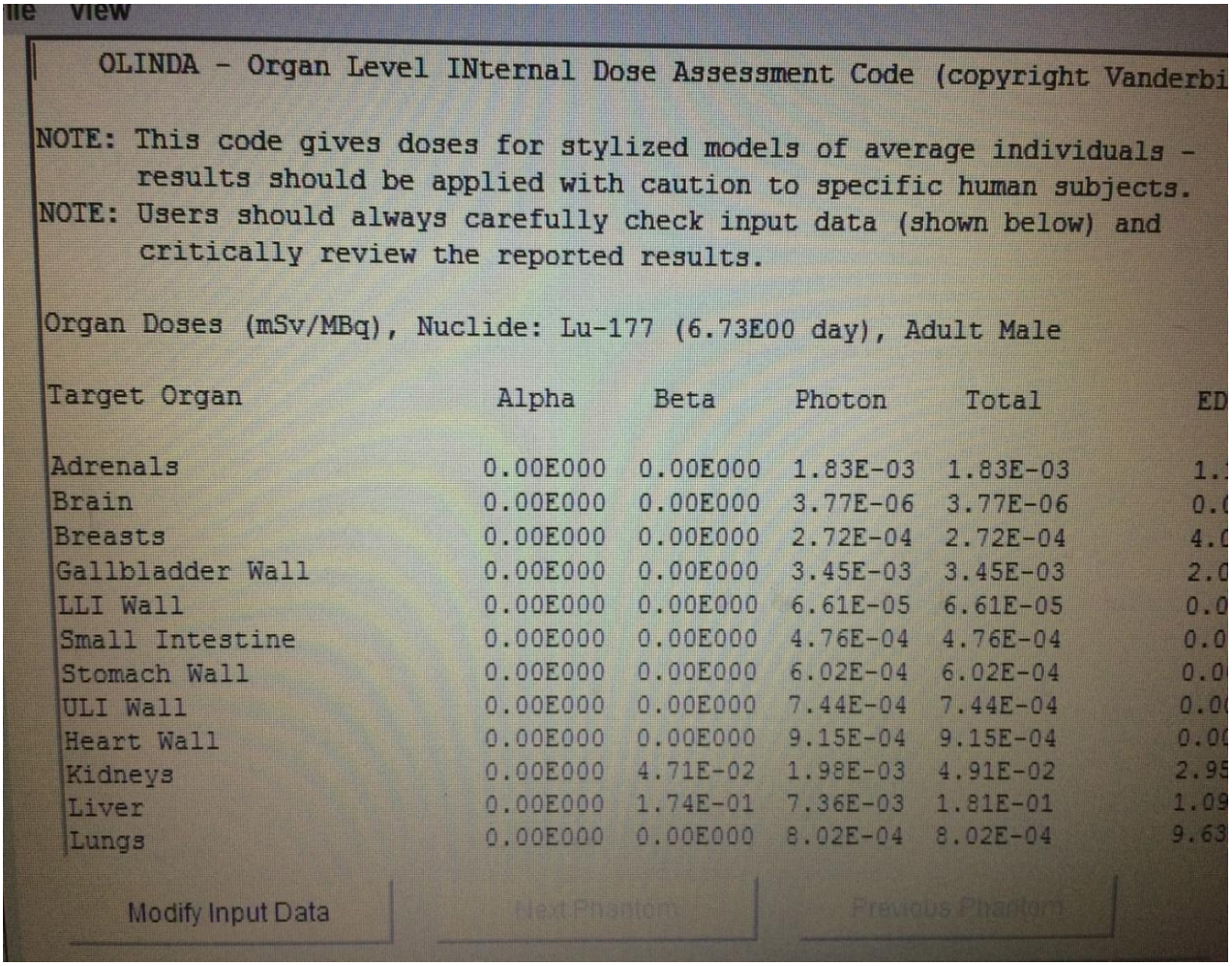



**Figure 6:** Liver uptake Percent Activity vs. Time curves

From the above results, resident times for the kidneys and the liver were calculated so that they can be recorded in OLINDA for dose in terms of mSv/MBq. Below is the equivalent radiation dose values as obtained from the OLINDA program.



File View

OLINDA - Organ Level INternal Dose Assessment Code (copyright Vanderbi

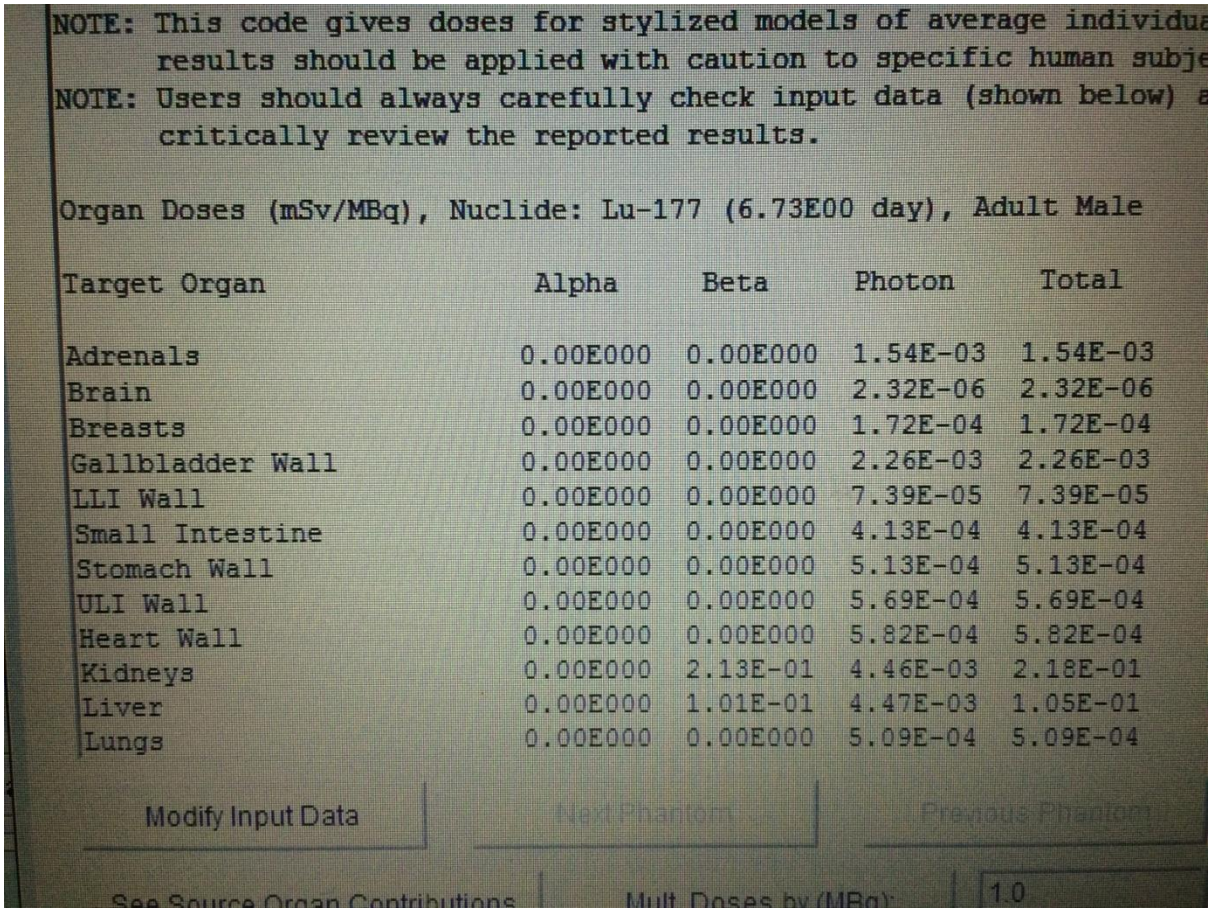
NOTE: This code gives doses for stylized models of average individuals - results should be applied with caution to specific human subjects.
NOTE: Users should always carefully check input data (shown below) and critically review the reported results.

Organ Doses (mSv/MBq), Nuclide: Lu-177 (6.73E00 day), Adult Male

| Target Organ | Alpha | Beta | Photon | Total | ED |
|---|---|---|---|---|---|
| Adrenals | 0.00E000 | 0.00E000 | 1.83E-03 | 1.83E-03 | 1.1 |
| Brain | 0.00E000 | 0.00E000 | 3.77E-06 | 3.77E-06 | 0.0 |
| Breasts | 0.00E000 | 0.00E000 | 2.72E-04 | 2.72E-04 | 4.0 |
| Gallbladder Wall | 0.00E000 | 0.00E000 | 3.45E-03 | 3.45E-03 | 2.0 |
| LLI Wall | 0.00E000 | 0.00E000 | 6.61E-05 | 6.61E-05 | 0.0 |
| Small Intestine | 0.00E000 | 0.00E000 | 4.76E-04 | 4.76E-04 | 0.0 |
| Stomach Wall | 0.00E000 | 0.00E000 | 6.02E-04 | 6.02E-04 | 0.0 |
| ULI Wall | 0.00E000 | 0.00E000 | 7.44E-04 | 7.44E-04 | 0.0 |
| Heart Wall | 0.00E000 | 0.00E000 | 9.15E-04 | 9.15E-04 | 0.0 |
| Kidneys | 0.00E000 | 4.71E-02 | 1.98E-03 | 4.91E-02 | 2.9 |
| Liver | 0.00E000 | 1.74E-01 | 7.36E-03 | 1.81E-01 | 1.0 |
| Lungs | 0.00E000 | 0.00E000 | 8.02E-04 | 8.02E-04 | 9.6 |

Modify Input Data | Next Phantom | Previous Phantom

**Image 1.** Equivalent radiation dose for cycle 1



NOTE: This code gives doses for stylized models of average individua
results should be applied with caution to specific human subje
NOTE: Users should always carefully check input data (shown below) a
critically review the reported results.

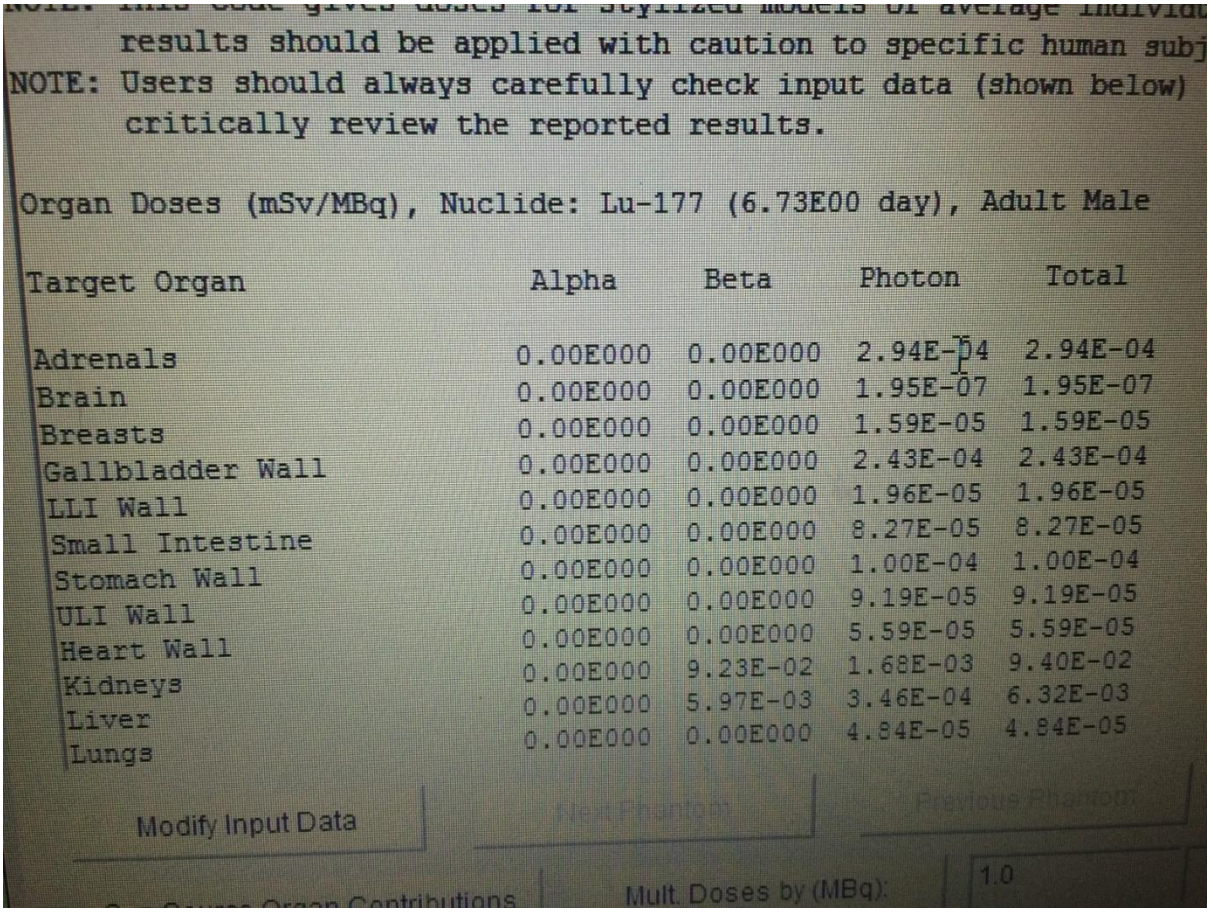
Organ Doses (mSv/MBq), Nuclide: Lu-177 (6.73E00 day), Adult Male

| Target Organ | Alpha | Beta | Photon | Total |
|---|---|---|---|---|
| Adrenals | 0.00E000 | 0.00E000 | 1.54E-03 | 1.54E-03 |
| Brain | 0.00E000 | 0.00E000 | 2.32E-06 | 2.32E-06 |
| Breasts | 0.00E000 | 0.00E000 | 1.72E-04 | 1.72E-04 |
| Gallbladder Wall | 0.00E000 | 0.00E000 | 2.26E-03 | 2.26E-03 |
| LLI Wall | 0.00E000 | 0.00E000 | 7.39E-05 | 7.39E-05 |
| Small Intestine | 0.00E000 | 0.00E000 | 4.13E-04 | 4.13E-04 |
| Stomach Wall | 0.00E000 | 0.00E000 | 5.13E-04 | 5.13E-04 |
| ULI Wall | 0.00E000 | 0.00E000 | 5.69E-04 | 5.69E-04 |
| Heart Wall | 0.00E000 | 0.00E000 | 5.82E-04 | 5.82E-04 |
| Kidneys | 0.00E000 | 2.13E-01 | 4.46E-03 | 2.18E-01 |
| Liver | 0.00E000 | 1.01E-01 | 4.47E-03 | 1.05E-01 |
| Lungs | 0.00E000 | 0.00E000 | 5.09E-04 | 5.09E-04 |

Modify Input Data | Next Phantom | Previous Phantom

See Source Organ Contributions | Mult. Doses by (MBq): 1.0

**Image 2.** Equivalent radiation dose for cycle 2



results should be applied with caution to specific human subj
NOTE: Users should always carefully check input data (shown below)
critically review the reported results.

Organ Doses (mSv/MBq), Nuclide: Lu-177 (6.73E00 day), Adult Male

| Target Organ | Alpha | Beta | Photon | Total |
|---|---|---|---|---|
| Adrenals | 0.00E000 | 0.00E000 | 2.94E-04 | 2.94E-04 |
| Brain | 0.00E000 | 0.00E000 | 1.95E-07 | 1.95E-07 |
| Breasts | 0.00E000 | 0.00E000 | 1.59E-05 | 1.59E-05 |
| Gallbladder Wall | 0.00E000 | 0.00E000 | 2.43E-04 | 2.43E-04 |
| LLI Wall | 0.00E000 | 0.00E000 | 1.96E-05 | 1.96E-05 |
| Small Intestine | 0.00E000 | 0.00E000 | 8.27E-05 | 8.27E-05 |
| Stomach Wall | 0.00E000 | 0.00E000 | 1.00E-04 | 1.00E-04 |
| ULI Wall | 0.00E000 | 0.00E000 | 9.19E-05 | 9.19E-05 |
| Heart Wall | 0.00E000 | 0.00E000 | 5.59E-05 | 5.59E-05 |
| Kidneys | 0.00E000 | 9.23E-02 | 1.68E-03 | 9.40E-02 |
| Liver | 0.00E000 | 5.97E-03 | 3.46E-04 | 6.32E-03 |
| Lungs | 0.00E000 | 0.00E000 | 4.84E-05 | 4.84E-05 |

Modify Input Data

Mult. Doses by (MBq): 1.0

**Image 3.** Equivalent radiation dose for cycle 3

Table 1 and 2 show the final calculated equivalent radiation dose (mSv/MBq) and absorbed radiation dose (mGy/MBq) for each patient's organ and the specific cycle, whilst Table 3 gives the overview of dose side by side for all cycles and organs.

**Table 1. Dose for all Kidneys**

| Patient no. | Cycle | Organ | mSv/MBq | Dose(Gy) |
|---|---|---|---|---|
| **1** | **1** | **Kidneys** | **0.0491** | **0.3633** |
| **2** | **2** | **Kidneys** | **0.218** | **1.6132** |
| **3** | **3** | **Kidneys** | **0.094** | **0.6956** |

Table 1 shows the difference in individual uptake of the radionuclide in different cycles.

**Table 2. Dose of the Liver for all Cycles**

| Patient no. | Cycle | Organ | mSv/MBq | Dose(Gy) |
|---|---|---|---|---|
| **1** | **1** | **Liver** | **0.181** | **1.3394** |
| **2** | **2** | **Liver** | **0.105** | **0.777** |
| **3** | **3** | **Liver** | **0.00632** | **0.0468** |

Table 2 show the importance of dosimetry, this is shown by the low dose being absorbed by the tumor site (Liver cycle 3), which shows the reduction of the tumorwhich correlates with the reduction of the radionuclide uptake.

**Table 3. Dose comparison of all organs**

| Patient no. | Cycle | Organ | Dose(Gy) |
|---|---|---|---|
| **1** | **1** | **Kidneys** | **0.3633** |
| | | **Liver** | **1.3394** |
| **2** | **2** | **Kidneys** | **1.6132** |
| | | **Liver** | **0.777** |
| **3** | **3** | **Kidneys** | **0.7548** |
| | | **Liver** | **0.6956** |

The dose tables and images show the contrast in individual dose to organs for individual patients, Results will be discussed in detail in the next chapter'

## CHAPTER 5: DISCUSSION

According to the standard dosimetry, kidneys are the dose limiting organs together with the bone marrow Kwekkeboom D, *et al* [2008][18]. It is stated that the kidneys must not get more than 25 Gy for the whole therapy (multiple cycles summed up) and the bone marrow 2 Gy, these are the limits that indicate the likelywood of occurrence of severe effects from radiation after therapy within 5 yrs Kwekkeboom D, *et al* [2008]. In this study we concentrated on the kidneys as well as the tumor region (liver) and the absorbed doses for a single cycle, based on the planar conjugate image method. Figure 5 shows the time activity curve for the summed kidney data for each patient in a particular cycle. As is apparent, cycles 1 and 3 had a similar curve in clearance (these show that by the time we imaged for these patients, the uptake phase of the pharmacokinetics had already been completed and only the clearance phase was imaged), whilst for cycle 2 the last stage of uptake was caught together with the early clearance phase. This showed that the uptake of the radionuclide occurs within the 5 hrs post infusion, cycle 1 and 3 clearance started earlier than cycle 2 but still showed the radionuclide clearance starts very early (within 5 hrs). In figure 6, the liver activity percentage vs time was plotted, again from the analysis of the curve it is clearly seen that in cycle 1 the clearance phase was imaged. Whilst in cycle 2 the uptake stage was shown, in cycle 3 a small late uptake phase was seen before the clearance started. Garkavij M, *et al* [2009] suggested that for such a treatment, the 1$^{st}$ two cycles are the most effective as can be seen from the liver dose that cycles 1 and 2 had higher doses than cycle 3 (although different patients with differing cycles were used, this trend was visible even in this cohort). The lower dose in later cycles can be attributed to the lower tumor burden as the treatment lowers and shrinks the metastases. It would be interesting to observe a longer time frame than 24 hrs clearance (early stage of our dose measurements) to be able to get both the early stage and late stage of the radionuclide clearance by the kidneys and the decay and clearance in the liver (tumor region).

Images 1, 2 and 3 display the equivalent radiation dose from OLINDA/EXM™ after the input of the summed kidney residence times (the kidney activities are summed because OLINDA/EXM™ only displays the sum of the kidney dose rather than the individual left right kidney) and liver (tumor region) residence times have been entered. OLINDA/EXM™ takes into account the radionuclide and which type of particle it produces (for Lu-177, beta emission is the dominant interaction. The total equivalent radiation dose will be displayed and its units being mSv/MBq, this equivalent radiation dose can then be converted to dose in a particular organ of interest. Multiple organs are displayed by OLINDA/EXM™ and there seems to be dose in those organs,

this is because of the fact that OLINDA/EXM™ uses the MIRD schema which takes into account a particular organ as both a source and also a target by surrounding organs.

Tables 1 and 2 show the organs that were studied and their absorbed dose in Grays (Gy) for each organ, the kidneys received variable doses for each cycle ranging from 0.363 to1.61 Gy. This is individually based as each patient has their specific pharmacokinetics, which differ from individual to individual. From the results it is evident that cycle 2 received a significantly higher dose to the kidneys than the other cycles, but for the dose to the liver (tumor region) the $1^{st}$ cycle received more compared to the other cycles. The liver (tumor region) received doses ranging from 0.636 to1.613 Gy, again the emphasis on the contribution per cycle for target (Liver tumor) organ for the start of the treatment and $3^{rd}$-$4^{th}$ cycles. As PRRT is a palliative (treatment that is used to improve quality of life for the patient and reduce tumor burden without any possibility of curing) rather than a curative (usually a radical approach to cure) treatment, it is a balance to decide whether 2 cycles would work better than 4 or more. Mostly the patient will give feedback on the quality of life during treatment and physicians, patients and physicists must always work together for the treatment to have a positive impact.

## CHAPTER 6: CONCLUSION

Individualised internal dosimetry includes a lot of estimations and processes, when done; it is of importance to note that each individual responds differently to the same stimuli in the body. Results of this research work show how dose limiting organs can be evaluated and precautionary measures taken to reduce the risk of radiation effect. Planar conjugate imaging is a good start to understand internal dose calculations. It has been shown by many authors that planar image dosimetry tends to overestimate the dose to organs, and that newer modalities such as SPECT (Single Positron Emission Computed Tomography) tend to show slightly lower doses than planar dosimetry. It is still acceptable for one to have planar dosimetry. In South Africa this dosimetry of patients undergoing Lu-177 therapy is relatively new, and with more hospitals offering the therapy it will be of use for physicists to get accustomed to individualized dosimetry and to also work in getting SPECT dosimetry as this would reduce the number of scans and the time interval with which dosimetry can be done. From the results it must be noted that some of the fields to be looked at in the future would be to account for all the dose in the body (if 7400 MBq is injected, how much of it is in the body), also another suggestion was how would the dose be affected if the $1^{st}$ scan is done before the patient excretes the urine ($1^{st}$ scan taken when all activity is in the body) and calibration factor calculated from this $1^{st}$ scan. Future studies will be looked at in terms of moving towards utilizing SPECT imaging to determine dose. The objectives of our study were to get acquainted with the MIRD schema and usage of OLINDA/EXM™ and also to be able to calculate organ dose for some patients undergoing PRRT with $^{177}$Lu-DOTATE. A broader study with more patients and their whole treatment cycle would be able to show the comparability of the results to others which were done with more cycles, longer time intervals (which at the time of the research were not possible due to the logistical and financial burden on patients who came from different provinces) would be able to give a much broader view of the study. From the work that was done during this research period, it has been possible to set up an individualized patient dosimetry system at another hospital and help add into the pool for physicists to learn and hopefully be able to improve on the techniques for the betterment of the patient treatment and importantly for the safety of all who work with these radionuclides. In work to subsequently follow, the use of SPECT/CT to get a more accurate dose measurement is to be investigated with the view of improving radionuclide dose measurement and to improve on the planar method.

## REFERENCES


[1] Sandström, M. (2012). Dosimetry of Radionuclide Therapy with $^{177}$Lu –Octreotate, Digital Comprehensive summaries of Uppsala dissertations from the faculty of medicine 707.

[2] Loevinger R., Budinger T.F. and Watson E.E. (1988). MIRD Primer absorbed dose calculations, ISBN 0-932004-25-3.

[3] Sandström, M., Garske-Román, U., Granberg, D., Johansson, S., Widström, C., Eriksson, B., Sundin, A., Lundqvist, H. and Lubberink, M. (2013). Individualized Dosimetry of Kidney and Bone Marrow in Patients Undergoing $^{177}$Lu-DOTA-Octreotate Treatment, *J Nucl Med.* 2013;54:33-41Doi: 10.2967/jnumed.112.107524. Online ISSN: 2159-662X

[4] Schuchardt, C., Kulkarni, H., Zachert, C. and Baum, R. (2013). Dosimetry in Targeted Radionuclide Therapy: The Bad Berka Dose Protocol-Practical Experience, 10.5005/jp-journals-10028-1058.

[5] Amato, E., Campennì, A., Herberg, A., Minutoli, A. and Baldari, S. (2011). Internal Radiation Dosimetry: Models and Applications, 12 Chapters on Nuclear Medicine, Dr. Ali Gholamrezanezhad (Ed.), ISBN:978-953-307-802-1.

[6] Mjekiqi, L.E. (2013). Estimation of the absorbed dose to patients treated with $^{177}$Lu-Dotatate with regards to the long-term retention and radionuclide impurity in the form of $^{177m}$.

[7] Kam, B.L.R., Teunissen J.J.M., Krenning E.P., de Herder W.W., Khan S, van Vliet EI, Kwekkeboom DJ. Lutetium-labelled peptides for therapy of neuroendocrine tumours, Eur J Nucl Med Mol Imaging 2012; 39: (Suppl 1).

[8] https://en.wikipedia.org/wiki/Ionizing_radiation accessed on 10/08/2015

[9] Sathekge, M. (2013). Targeted Radionuclide therapy, 289 *CME*

[10] Guerriero, F. (2013). Kidney dosimetry in $^{177}$Lu and $^{90}$Y peptide receptor radionuclide therapy: Influence of image time integration method, and risk factors.

[11] Garkavij, M. (2010). $^{177}$Lu–Octreotate Therapy in patients with Disseminated Neuroendocrine Tumours: Analysis of Dosimetry with impact on future Therapeutic Strategy

[12] Zanconico, P.B.and Divgl C. (2008) Patient-Specific Radiation Dosimetry for Radionuclide Therapy of Liver Tumours with Intrahepatic Artery $^{188}$Rhenium.*Lipiodol*, Semin Nucl Med 38:S30-S39 © 2008 Elsevier Inc.

[13] Baka, I., Ploussi, A., Argyrou, M., Valasi, A., Limouris, G.S. and Lyra, M. (2015). Value of Individualized Dosimetry in Peptide Receptor Radionuclide Therapy (PRRT) by $^{177}$Lu{Dota0, Tyr3] Octreotate, *e-Journal of Science & Technology (**e-JST**). Accessed on 23 May 2015.*

[14] Rojo, A.M. (2008). International Radiation Protection Association, 12$^{th}$ International Congress, Buenos Aires, Argentina. Seminar I Radiological Protection in Nuclear Medicine.

[15] Kwekkeboom, D. Herder, W. Kam B (2008). Treatment With the Radiolabeled Somatostatin Analog [177Lu-DOTA0,Tyr3] Octreotate: Toxicity, Efficacy, and Survival.