INSTITUTO POLITÉCNICO DE LISBOA

ESCOLA SUPERIOR DE TECNOLOGIA DE SAÚDE DE LISBOA

TOWARDS PERSONALISED NUCLEAR MEDICINE – PATIENT-SPECIFIC OPTIMISATION OF ADMINISTRATED ACTIVITY AND ACQUISITION TIMES FOR ^{68}Ga-DOTATOC PET IMAGING

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Mestrado em Radiações Aplicadas às Tecnologias de Saúde- Especialização em Imagem Molecular e Multimodal

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Author’s Declaration of Originality

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I hereby certify that I am the sole author of this thesis, to the best of my knowledge.

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Abstract

Background: ^{68}Ga-DOTA-Somatostatin Analogues (SSA) Positron Emission Tomography/Computed Tomography (PET / CT) presents itself as the gold standard technique in neuroendocrine tumours (NET).

The optimization of the activity to be administered has never merited a more in-depth study until the beginning of 2020.

The aim of this study is to analyse the influence of Body Mass Index (BMI) in Image Quality (IQ) and purpose a new dose regimen based in this patient characteristic.

Methods: From March 2020 until July 2020, 81 patients performed a ^{68}Ga-DOTATOC PET/CT at Nuclear Medicine (NM) in University Hospitals Coventry Warwickshire (UHCW). UHCW protocol requires an administration between 100-200 MegaBequerel (MBq) with the scan being performed 45-60 minutes after injection. In this study, patients' characteristics were considered, and BMI was calculated for each patient. 2 experienced NM Technologists visually graded IQ using a 4-point scale. Patients were finally divided into IQ score and BMI categories to achieve a dose regimen.

Results: Activity/BMI was proven to have the best correlation to achieve a dose regimen according to linear regressions and statistical tests. Visual assessment show that higher BMI were classified with lower IQ and the influence of this patient characteristic was proven, however no one was classified as IQ1-Non-Diagnostic.

IQ 3 was chosen instead of IQ 4 to derivate the dose regimen expression because IQ 3 were considered moderate IQ which means that the clinical question can still be answered (avidity for somatostatin receptors in NET tumours) without exposing the patient to unnecessary radiation, following ALARA principle.

Non-linear expression was derived to calculate the dose regimen for both observers.

Conclusion: BMI has a major influence in IQ and can be used to obtain a dose regimen. The purpose regimen tries to uniformise the IQ for all the BMI categories without diminishing diagnostic accuracy and following ALARA principles.

Keywords: ^{68}Ga-DOTATOC PET/CT, Neuroendocrine Tumors, Image quality, PET/CT, Optimization, Body Mass Index

Resumo

Introdução: ^{68}Ga-DOTA-Análogos da Somatostatina Tomografia por Emissão de Positrões / Tomografia Computadorizada (PET/CT) apresenta-se como a técnica de primeira linha nos tumores neuroendócrinos (NET). A otimização da atividade a administrar nunca mereceu um estudo mais aprofundado até ao início de 2020.O objetivo deste estudo é analisar a influência do Índice de Massa Corporal (IMC) na Qualidade de Imagem (QI) e propor um novo regime de dose baseado no IMC.

Métodos: De março a julho de 2020, 81 pacientes realizaram PET / CT ^{68}Ga-DOTATOC no departamento de Medicina Nuclear (MN) no centro hospitalar universitário de Coventry e Warwickshire (UHCW). O protocolo UHCW requer uma administração entre 100-200 MegaBequerel (MBq) com imagens realizada 45-60 minutos após a injeção. Neste estudo, as características dos pacientes foram consideradas e o IMC foi calculado para cada paciente. Dois técnicos experientes em MN avaliaram visualmente a QI usando uma escala de 4 pontos. Os pacientes foram finalmente divididos em pontuação de QI e categorias de IMC para atingir um regime de atividade a administrar.

Resultados: A atividade / IMC demonstrou ter a melhor correlação para atingir um regime de dose de acordo com regressões lineares e testes estatísticos. A avaliação visual mostra que maior IMC foi classificado com menor QI e a influência dessa característica do paciente foi comprovada, porém nenhum paciente foi classificado como IQ1-Não Diagnóstico.IQ 3 foi escolhido em vez de IQ 4 para derivar a expressão do regime de dose uma vez que o IQ 3 foi considerado IQ moderado, o que significa que a questão clínica ainda pode ser respondida (expressão dos recetores de somatostatina em tumores NET) sem expor o paciente a radiação desnecessária, seguindo ALARA princípio. A expressão não linear foi derivada para calcular o regime de dose para ambos os observadores.

Conclusão: o IMC tem uma grande influência no QI e pode ser usado para obter um regime de dose. O regime de dose tenta uniformizar o IQ para todas as categorias de IMC sem diminuir a precisão do diagnóstico e seguindo os princípios ALARA.

Palavras-chave: ^{68}Ga-DOTATOC PET / CT, Tumores neuroendócrinos, Qualidade de imagem, PET / CT, Otimização, Índice de Massa Corporal

Table of Contents

List of Tables

List of Figures

List of Abbreviations

^{111}I	Indium - 111
^{123}I	Iodine - 123
^{15}O	Oxygen - 15
^{177}Lu	Luthetium - 177
^{18}F-FDG	2-deoxy-2-[fluorine-18] fluoro-D-glucose
5-HIAA	5-hydroxyindole acetic acid
^{68}Ga	^{68}Gallium
^{68}Ge	^{68}Germanium
^{90}Y	^{90}Itrium
^{99m}Tc	^{99m}Technetium
β	Beta emitter
γ	gamma emitter
ºC	Celsius Degree
AAA	Advanced Acellerator Applications
AC	Attenuation Correction
ALARA	As Low As Reasonably Achievable
BMI	Body Mass Index
CgA	Chromogranin A
cps	Counts per Second
CT	Computed Tomography
d	Days
DCGs	Dense-Core Granules
DES	Diffuse (Neuro)Endocrine System
DOTA	Tetraazacyclododecanetetraacetic
DTPA	Diethylenetriaminepentaacid
EANM	European Association of Nuclear Medicine
EMA	European Medicines Agency
FDA	Food and Drugs Administration
FOV	Field of View
GE	General Electric
GI	Gastrointestinal
G	Good

h	Hour
ICRP	International Commission on Radiological Protection
IQ	Image Quality
IRMER	Ionising Radiation Medical Exposure Regulations
keV	Kiloelectronvolt
kg	Kilos
kBq	KiloBequerel
LOR	Line of Response
mA	Milliamperes
MBq	MegaBequerel
MeV	MegaelectronVolt
min	Minutes
mm	Millimetres
mm^2	Square millimetre
mm^3	Cubic millimetre
MN	Nuclear Medicine
M	Moderate
MRI	Magnetic Resonance Imaging
mSv	Millisieverts
NE	Neuroendocrine
NECs	Neuroendocrine Carcinomas
NENs	Neuroendocrine Neoplasms
NETs	Neuroendocrine Tumours
ND	Non-Diagnostic
ns	Nanoseconds
PACS	Picture Archiving and Communication Systems
PET / CT	Positron Emission Tomography/Computed Tomography
P	Poor
PRRT	Peptide Receptor Radionuclide Therapy
PVE	Partial Volume Effect
RARECARE	Rare Cancers in Europe Project
SNMMI	Society Nuclear Medicine and Molecular Imaging
SNR	Signal-to-Noise Ratio
SPECT	Single Photon Emission Computerized Tomography
SSA	Somatostatin Analogues

SST	Somatostatin
SSTRs	Surface Somatostatin Receptors
SUV	Standard Uptake Value
Syn	Synaptophysin
TNM system	-Tumour -regional Nodes -distant Metastasis system
TOF	Time of Flight
UHCW	University Hospitals Coventry and Warwickshire
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

Chapter I- Introduction

Positron Emission Tomography/Computed Tomography (PET/CT) is an essential tool in the Medical Imaging world. The first radionuclide use in clinical practise was ^{18}Fluor (^{18}F)- 2-deoxy-2-[fluorine-18] fluoro-D-glucose (FDG) because of the high afinity and consequent accumulation in cells with high glycolitic proliferation, helping diferenciating bening from malignant patology and having a better understanding of the tumor physiological behaviour.[1]

Over the years new radionuclides have been tested and commercialized which is the case of Oxygen-15 (^{15}O) or Carbon-11 (^{11}C). However some problems arised from these unconventional radionuclides like the short half life which made it difficult to transport from production site to Nuclear Medicine (NM) departments.[2]

NM has always had an important role in the most diverse primary oncologic site- from glioblastomas to melanomas through the most common cancer such as breast or prostate cancer.[2]

Even in rare cancers like is the case of Neuroendocrine Neoplasms (NEN), NM have they say with conventional NM scans. However, this conventional NM scans have some limitations such as low spatial resolution, high level of intestinal uptake or long waiting times from injection to scan. [3]

That is why the development of a PET/CT radionuclide that can be use in NEN was a game changer in this oncological field.[4]

Gallium-68 (^{68}Ga) - tetraazacyclododecanetetraacetic (DOTA) - Somatostatin Analogues (SSA) PET/CT presents itself as the gold standard technique for (re)staging, localization of the primary tumour and response to therapy in NEN.[4]

Several protocols have been published over the years, improving aspects such as patient preparation, however, the optimization of the activity to be administered has never merited a more in-depth study until the beginning of 2020 when the first article on this topic was published.[5]

This dissertation is divided in 4 different chapters.

Chapter I is an introduction to the theme and the importance of it in the NM departments as well as for patients that undergo this investigation.

In this chapter is also cover the objectives for this dissertation, being divided in geral and more specific ones.

Chapter II is a state of the art about the subject in study. First a quick approch to NEN is performed, given the reader the opportunity to understand how this neoplasies are categorized, how this caracterization has change within the years and the evolution of medicine and a epidemiologic view around the globe from different studies performed by different scientists in different years.

Another subject that is described in this chapter is how the imagiologic techniques have such an important role in the diagnose of this neoplasy and how different techniques can show different aspects providing the most accurate diagnosis and consequently the best therapeutical approach.

Is in this segment, that a comparasion between different NM techniques can be found and explaining each one, have the best outcome in terms of radiation protection and diagnosis accuracy. A quick mention to how NM can be helpul in terms NEN therapy can be found in here, explaining which radionuclides can be used.

After a more clinical approach, the next point focus more in the physics part of this dissertation, explaining briefly how PET/CT works and how some patient and equipment parameters can influence the quality of the final image and consequently the diagnosis.

The final focus on this second chapter is to understand the physical particularities of ^{68}Ga and why is it gain more and more importance for the NM area and also the differents ^{68}Ga-DOTA-SSA that can be found in the market and the differences and similarities among them.

After a explanation how the ^{68}Ga-DOTA-SSA PET/CT is performed and which information is required to go head with the scan. Is also mention what is normal distribution for this radiopharmaceutical and how the image acquisition is done.

One of the most important topic is topic number 2.2.3 where the reader will have a better understanding why is so important to have a activity administration based on patients’ characteristics and which work have been done to achieve this goal.

Chapter III presents the material and methods used to performed this dissertation, which includes characterization of the sample, inclusion and exclusion criterias, brief description of the equipment, methodology used, statistical analyses and ethical considerations.

Chapter IV is where the results of this investigations are presented to the reader using graphic elements.

Chapter V is called discussion giving the reader an opportunity to see other studies performed in this field and the conclusions.

Chapter VI presents a brief conclusion of this dissertation enlighting new prespectives that can be study in a near future.

Chapter VII is dedicated for the bibliography used to support this dissertation and in chapter VIII the reader can find attachments relevant for the project.

1.1 Theme Relevance

NM centres that practice this technique still follow the protocol of administration of an activity between 100-200MegaBequerel (MBq) regardless of the patient's physical characteristics, more specifically the weight and body mass index (BMI).

One of the major problems with this standardized administration is the non-application of the As Low As Reasonably Achievable (ALARA) principle, since patients with less weight/BMI are being exposed to a higher dose of radiation than necessary to achieve good image quality (IQ) and, on the other hand, patients with more weight/BMI have images that sometimes become difficult to analyse due to poor quality.

Consequently, it is also necessary to think that patients with the same weight may not have the same BMI, which can lead to a greater / lesser attenuation of radiation.

Many studies have been carried out using ^{18}F - FDG, however the results obtained cannot be extrapolated directly to ^{68}Ga-DOTA-SSA, since the range of the particles and their energy is different.[5]

Other important topic to be analyse in this project is how time between injection and scanning can affect IQ. Because according to the guidelines and UHCW protocol scans need to be performed 45-60 minutes after injection, however in the routine practice, delays are constantly happening, sometimes do to patients needs (extra time in the PET/CT room due to the patient being a pat -slide, a more elderly/fragile patient that needs extra attention and care while leaving the scanning room or a patient that is claustrophobic so extra reassurance needs to be given to patient, so the scan can be performed) or equipment problems (CT lasers stop working,bed not moving to starting position,power-cuts).

That is why more studies must be carried out to continue moving towards a personalized NM.

1.2 Objectives

The main objective of this study is to evaluate the influence of the patient's BMI on the IQ when performing a PET/CT with ^{68}Ga-DOTATOC and to propose a method of calculating the activity for the IQ which better respond to the clinical question in this context always keeping in mind radition protection measures.

The specific objectives are to: a) assess how the patient’s characteristics influence the IQ b) determine the relationship between the BMI and the activity to be administered; c) analyse the association between BMI, the activity administered and IQ purposing a new dose rigemen; d) acess how acquisition times (time between injection and scanning) have influence in IQ.

Chapter II - State of the Art

2.1 Clinical Background

2.1.1 Neuroendocrine System

The Neuroendocrine (NE) System often referred as the diffuse (neuro)endocrine system (DES) is the combination of two majors' systems, the Neuronal and Endocrine.[6] The "neuro" property is defined by rapid transfer of short-term events and their coordination through chemical information.[6] In the case of DES, dense-core granules (DCGs) take a relevant role being defined as organelles that store, transport and regulate the release of several important peptides and proteins like monoamines, similar to the DCGs present in serotonergic neurons, however DES cells do not have synapses.[6–8] On the other hand, the "endo" property is involved in the integration and coordination of long-term events, such as synthesis and secretion of these monoamines [6,7].

The DES is composed of NE cells scatters throughout the body. They are mainly found scattered in the gastrointestinal (GI) tract (including the small intestine, rectum, stomach, colon, oesophagus and appendix), the gallbladder, the pancreas, and the thyroid. NE are also commonly found in the lungs or airways into the lungs (bronchi), as well as the respiratory tract of the head and neck.[6–9] The pituitary gland, the parathyroid glands and the inner layer of the adrenal gland (adrenal medulla) are almost all made up of NE cells.[6] Other sites of NE cells include the thymus, kidneys, liver, prostate, skin, cervix, ovaries and testicles. NE cells can be either isolated (pituitary gland) or grouped to form aggregates, such as the islets of Langerhans in the pancreas or the neuroepithelial bodies in the bronchopulmonary tract.[6–8]

2.1.2 Neuroendocrine Neoplasms – Epidemiology, Anatomy, Physiology, and Classification Criteria

NENs present themselves as a heterogeneous group of neoplasms, which have their origin in the cells of the NE system, thus presenting different clinical behaviours.[7,8,10,11] Although still considered rare tumours up until 10 years ago, the most recent data indicates the incidence of NENs has increased exponentially over the last 4 decades and they are as common as Myeloma, Testicular Cancer and Hodgkin's Lymphoma.[7,9,11,12] In terms of prevalence, NENs represent the second most common GI malignancy after colorectal cancer. Consequently, many experts are now claiming NENs are not rare.[7,13]

NEN compromise approximately 2% of all malignancies and about 0,5% of all newly diagnosed in the United States of America (USA). In 2019, a study revealed that the annual incidence of NEN was 1.09 per 100.000 persons in 1973 and increased to 6.98 per 100,000 persons by 2012.[7,14,15]

The increase in the incidence of NEN from 1973 to 2012 occurred across all sites, stages, and grades.[15] Reflecting the rising incidence and indolent nature of NENs the prevalence increased substantially from 0.006% to 0.048% in 2012. Many studies have been conducted in different countries of Europe, however the same can not be said about studies which include the entire continent.[15] One of the few studies published was the Rare Neuroendocrine tumours: Result of surveillance of Rare Cancers in Europe Project (RARECARE).[13] RARECARE included data between 1978 and 2002 from 27 different countries.[13] The incidence rate was 25 per 100.000 and the estimated complete prevalence of people which would be alive at the beginning of 2008 was 21 per 100.000.[13]

More recently, studies have been carried out in countries around Europe, for example in Spain a research was conducted where all the data related to NEN between 2010 and 2015 was analysed.[14] In this 5-year period was observed a significant increased in new diagnosed case from 975 (2010) to 1922 (2015), with an increasing tendency over the years. [14]

In 2019 was published data related to the incidence of NEN in the United Kingdom (UK) between 2013 and 2015. The UK incidence was 8.6 per 100.000 (2013-2015 combined). It increased steadily, from 3.9 cases per 100.000 in 2001 to 7.9 per 100.000 in 2012 in England.[12]

Given the body-wide distribution of NE cells, NENs have been described in the central nervous system, respiratory tract, GI tract, thyroid, skin, breast, and urogenital system(kidney, bladder, cervix, ovaries/prostate).[11] Most of the NEN raised from the GI tract, at the level of the bronchopulmonary system and in the pancreatic system, figure1.[7,8,11–13] It should be noted that in about 15% of patients diagnosed with NENs, the primary location is not found.[7]

Figure 2.1 illustrates the distribution of NEN.

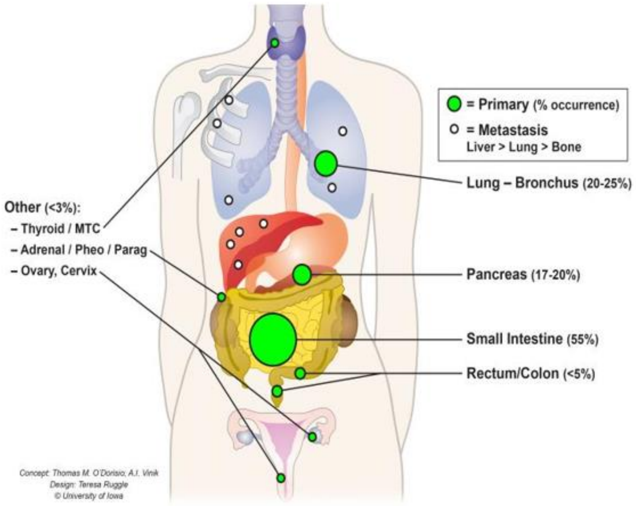


Figure 2.1 Anatomical Distribution of Neuroendocrine Neoplasm Fonte: *(https://uihc.org/health-topics/what-neuroendocrine-cancer)*

NENs are generally categorized based on histology (well differentiated versus poorly differentiated), proliferation rate (Ki 67 index and Mitotic Rate – to determinate the grade), clinical behaviour (functioning versus non-functioning) and stage.[7,8,10,11] Differentiation, grade, and stage are totally different concepts and critical to predict the outcome and guide therapy.[7,11]

The term NEN encompasses well – differentiated neuroendocrine tumours (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). NECs represent only 10-20% of all NENs. There are some areas of the body where almost all NENs are NETs (e.g. small intestine, ovary, parathyroid, pituitary) another organs NECs predominate (e.g. lungs, colon).[7–9,11]Differentiation refers to how closely the neoplastic cells resemble their nonneoplastic counterparts in the tissue from which they arose. Well differentiated NETs cells are described as cells which produce abundant secretory granules with intense immunoexpression of NE markers such as chromogranin (CgA) and synaptophysin (Syn). These cells are also characterised for being in a well – developed ‘organoid’, where the tumours cells are small with relatively uniform round to oval nuclei, a pattern often described as ´salt and pepper’. On the other hand, NECs demonstrate a solid proliferation of tumours cells with irregular nuclei, high mitotic features, and less cytoplasmic secretory granules.[7,8]

Up to 40% of NECs contain elements of non-NE histology, by definition, the NE component must exceed 30% for the tumour to be called NEC: otherwise it is classified as a mixed adenoneuroendocrine carcinoma.[11]

According to its grade, the classification of NENs is performed through the Ki-67 Index and mitotic rate. The Ki-67 index is a protein that is found in high concentration when the cell prepares to divide during the mitosis process (process used by healthy cells and tumor cells to divide and proliferate).[7,8,11,13] If in a certain anatomical location there is a high percentage of Ki-67, this means that the cells are dividing very quickly.[7,8] So, this Index can be described as an indicator of how fast tumor cells are multiplying.[7,8,11] Therefore, NENs tumors can be classified as G1, G2 or G3, table 2.1, where higher the G, higher the rate of growth and aggressiveness.[7,8,10,11] The mitotic rate is classified as how fast cancer cells are dividing and growing. The mitotic rate should usually be expressed as mitoses per millimeter per square (mm^2) area, ideally counted in up to $10mm^2$ to assure accuracy although tissue availability may restrict areas available for counting. That is why small biopsies sites may not use this measurement. As per Ki-67, as higher is the mitotic rate more aggressive will be the tumour.[16]

Table 2.1 World Health Organisation NEN classification 2017

Characteristic	Well-Differentiated (NET)			Poorly Differentiated (NEC)*
Grade	G1	G2	G3	G3
Ki-67 Index (%)	<3	3-20	>20	>20
Mitotic count (mm^2)	<2	2-20	>20	>20

NENs can be denominated as functional or non-functional, this designation is linked to the release of serotonin and other vasoactive peptides in the systemic circulation that will lead to the appearance of the carcinoid syndrome. The symptoms of carcinoid syndrome are flushing, usually on the head and upper chest, dysentery and abdominal cramps, wheezing, palpitations, telangiectasia, among others. In some NENs, this release may not be carried out in sufficient quantities to cause the symptoms described above, which are classified as non-functional NENs. [7–11]

Another important step in the characterization of the NEN is the staging, being define as the spread or extent of cancer in line with the primary Tumour (T) - regional Nodes (N) – distant, Metastasis (M) - system. NENs can be considered as either early stage (completely respectable) or advanced stage (either locally advanced and unresectable or metastatic).

2.1.3 Diagnose and Therapeutic Approach – Nuclear Medicine Contribution

NEN can be difficult to diagnose because of nonspecific clinical presentations. Common chronic symptoms include cough or diarrhoea, whereas others are clinically silent. A recent international survey of 1928 patients with NETs reported a mean delay of 52 months between symptom onset and diagnosis, patients see an average of six different consultants before receiving the correct diagnosis. When a physician suspects of NENs, laboratory test and imaging test are schedule to localise the primary (and perform a biopsy if possible), stage NEN and develop in concordance with a multi-disciplinary team an approach to reach curative or palliative states. CgA is the diagnostic biomarker of choice for NEN because it has a high sensitivity (5-91%) but low specificity (< 50%). Patients that feature with carcinoid syndrome a 24-hour (h)-urine 5-hydroxyindole acetic acid (5-HIAA) test should be ordered.[7,8,10,16,17]

There are two general categories of diagnostic imaging modalities that are used in combination for the diagnosis. The first modality is standard cross-sectional imaging with Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). CT constitutes the basic radiological methods for NEN imaging because of its wide availability, standardized reproducible technique and generally high diagnostic yield. The sensitivity of CT to detect NENs is 61-93% and the specificity is 71-100%. MRI is advantageous for examination of the liver and the pancreas and is usually preferred in the initial staging for the pre-operative imaging work-up. However, these modalities are limited its field of view (FOV) and is highly dependent on protocol choice.[4,16–18]

Functional imaging with radiopharmaceuticals is an important diagnostic tool because most of NENs have high cells surface somatostatin receptors (SSTRs) expression levels due to the somatostatin (SST) expression (SST is a small, cyclic neuropeptide that is present in neurons and endocrine cells). [4,7,16–18]

The first SSTRs imaging was performed in 1989 with a gamma-camera (γ-camera) using Iodine-123 (^{123}I)-Tyr3-octretotide, being the octreotide an SSA. Octreotide is produced synthetically because SST has a very short-half-life of around 3 min, which initially limited pharmacological use in the treatment of diseases.[18,19].

Due to several disadvantages such as a difficult radiolabelling procedure, high cost, limited availability of ^{123}I and considerable amount of intestinal activity accumulation complicating interpretation of images, ^{123}I was soon replaced by Indium-111 (^{111}I) bound to the peptide by means of the chelator diethylenetriaminepentaacid (DTPA).^{111}In-DTPA-octreotide became the most widely used radiotracer with varying sensitivity (67 - 100%), performing planar, Single Photon Emission Computerized Tomography (SPECT) and SPECT/CT imaging at 4, 24 and sometimes 48 h after injection. However, this diagnostic imaging presents some limitations such as relatively slow pharmacokinetics (scans have to be perform in different days and prolonged imaging protocols), physiologic uptake (that may restrict detection of small abdominal lesions)high-energy gamma (γ)-emissions (171 and 245 kiloeletroVolt (keV)), a medium-energy collimator must be used and spatial resolution is degraded compared to Technetium-99 metastable (^{99m}Tc) and unfavourable patient dosimetry limiting injectable activity to about 175 - 200 MBq, all resulting in relatively low-resolution images in comparison with PET/CT images.[4,8,10,16,18–20]

PET has significantly higher spatial resolution than γ-camera imaging. In the late 1900s a new PET agent, ^{68}Ga-DOTATOC (an SSA), was shown to rapidly localized NENs and imaging could be accomplished at 1h after injection, being the first clinical imaging carried out in 2001. Over the following years, ^{68}Ga-DOTA-SSA began to be widely used in Europe and several other countries. In a systematic review including 22 studies and 2015 patients ^{68}Ga-DOTA-SSA PET/CT had an excellent diagnostic accuracy with a 93% and 96% of sensitivity and specificity, respectively. The high sensitivity of ^{68}Ga-DOTA-SSA PET/CT is especially important for identifying patients with a metastatic NEN of unknown origin.16,18,21-23 (more information in Chapter 2.3.2)

However, high-grade tumours, especially NEC, originate from poorly differentiated cells commonly have low or absent SSTR expression and tend to have glycolytic and metabolic rates, being ^{18}F-FDG a better option for functional imaging.[21]

In fact, a strong association have recently been shown between worse outcome in patients with well-differentiated or low-grade tumours, and higher ^{18}F-FDG uptake.[17,21]

The mainstay of treatment is surgery with curative intent when NEN are localised with low regional lymph nodes involvement and in accessible place, however this can also be indicated for palliative debulking to decrease tumour burden or help control hormone production.[7,8,16,17]

The choice of the most appropriate treatment when in the presence of patients with inoperable or metastatic tumours is considered limited. The response to chemotherapy is between 20 - 35% effective in a minority of tumours characterized as poorly differentiated, being even ineffective in most well-differentiated tumours.[16,23] Among the

treatment options for the well differentiated, it important to highlight the pharmacological treatment since there is an increase in the expression of receptors of 5 subclasses of SSTRs, the most frequent being subclass 2 and 5. [7,10,16]
When these SSTRs are activated through SSA (as is the case with octreotide or lanperotide), anti-secretion and anti-tumour proliferation activity is observed.[16,17,19,23] These have the advantages of not only reducing the symptoms of the disease, but also reducing the proliferation of the tumour, that is why they are still known today as the first treatment line for NENs.[7,10,23] However, in some patients undergoing this therapy, the desired effects are not observed, that means, the tumour continues with a high proliferation rate and the peptide receptor radionuclide therapy (PRRT) is a second viable approach.[16,17,19,23]

PRRT has as its basic mechanism the use of a natural peptide, like the circulating peptide, somatostatin, which is combined with a radionuclide, changing its name to a radiopeptide. After the injection of the radiopeptide into the patient's bloodstream, it will bind to the cells of the NEN, depositing a high dose of radiation directly on the cancer cells.[7,8,16,19] All of this is due, as previously mentioned, to the great expression of SSTRs that extend from the cell to its surface and that will connect with SST.[8,16,19] In the case of PRRT, SSA are combined with a therapeutic dose of radionuclides. The most used are Itrium-90 (^{90}Y) and Lutetium-177 (^{177}Lu), table 2.2 shows some of the radionuclide's characteristics.[19,23]

Table 2.2 ^{90}Y versus^{177}Lu physics characteristics [19,23]

Radionuclides	Beta emitter (β) (MegaelectroVolt) (MeV)	Range (millimetres) (mm)	Half-life (days) (d)	Gamma rays (γ) (keV)
^{90}Y	2.27	10	2.7	----
^{177}Lu	0.477	2-4	6.7	133 (6,5%) 208 (11%)

Due to the greater energy and reach of the ^{90}Y particles, there is a greater radioactivity in the tumour cell per peptide molecule, which promotes a better distribution throughout the tumour, which becomes especially important in large tumours and tumours that have a distribution of very heterogeneous receptors. The half-life of ^{90}Y also leads to a higher dose rate. [16,17,23]

On the other hand, the particles emitted by the ^{177}Lu present a lower dose and range, promoting a better absorption in small tumours, also allowing an imaging evaluation soon after the realization of the therapy since it has the emission of γ rays allowing dosimetry study during the same.[7,16,17,23]

Because it has a longer half-life than ^{90}Y, ^{177}Lu allows for lower dose rates making it more convenient for transportation between the production site and the hospital where the therapy will take place, which often requires international trips lasting more than 1 day.[16,17,23]

Currently ^{177}Lu is the radionuclide of choice since it produces less nephrotoxicity when compared to ^{90}Y.[8,23]

2.2 Scientific Background PET/CT

2.2.1 Basic Principles of PET/CT

PET is a commonly used imaging tool because it allows a non-invasive and quantitative imaging of cellular and molecular events in patients, giving functional information in contrast to morphological information obtained from CT or MRI.[24,25]

For the imaging method, PET tracers which are biological molecules or sometimes artificial building blocks for specific targets labelled with positron emitters (most common ^{18}F followed by ^{68}Ga) are intravenously injected into the patient. The radioactive atom of the radiotracer emits positrons. The emitted positron combines with an electron after travelling a distance up to several millimetres (mm) in tissue. The positron and electron are then converted into two photons, each having energy of 511 keV, which are emitted in nearly based on the simultaneous (coincidence) detection of these two photons. A PET scanner consists of many photon detectors surrounding the patient. Each detector is a few mm size and a group of them formed into a block that is typically connected to a group of four photomultiplier tubes. The scintillator detectors convert incoming photons into light before amplifying the signal using the photomultiplier tubes. When there is a positron emission within the ring of detector, the two 511 keV photons, travelling at the speed of light, will be detected almost instantaneously (within approximately 10 nanoseconds (ns)). During a PET scan millions of photons arriving at different detectors are collected within this coincidence timing window, providing information about the distribution of the radiotracer in tissue. [24–27]

The line between the two detectors that detected each coincidence event is called line of response (LOR).[25]

Typically, data are collected over several minutes (min) and all detected coincidence events are grouped into parallel LOR to form projections through the patient that are used for image reconstruction, typically using iterative reconstruction techniques. [25]

One of the advantages of this type of localisation when comparing to SPECT is, not requiring collimators to provide positional information and therefore offering much higher sensitivity.[24,26]

The type of events described above are so called ‘true events’, however not all coincidences contribute to the signal. Background noise is added to the signal due to photons that are coincidence detection of two uncorrelated photons (random coincidences) or by scattered before detection.[24–27]

The differences between true, random and scatter coincidences are illustrated in figure 2.2. True coincidences (figure 2.2 a) arise from the simultaneous (coincident) detection of two annihilation photons generated by one positron emission. Ideally, only true counts are detected. A large fraction of the emitted photons (up to 50%) is scattered before leaving the patient. When one of the photons has been scattered, it will result in a dislocation from the ‘true coincidence’ detection, figure 2.2 c. The proportion of random events from the total coincidence events increases significantly with higher activity concentrations and large coincidence acceptance time windows for example moving from 10 to 15 ns (figure 2.2 b).[24–28]

Moreover, when two photons from two different positron emissions are accidentally (randomly) detected simultaneously (while the others are undetected), the PET camera will notice a random coincidence detection. These random coincidences result in image distortions (appearing as the addition of a smooth background). The fraction of coincidence events that can be attributed to scatter increases with increased scattering material for example larger and denser tissue. Although unwanted coincidences can degrade IQ, all modern image reconstruction techniques use correction algorithms, which limit the effect of these types of events.[24–28]

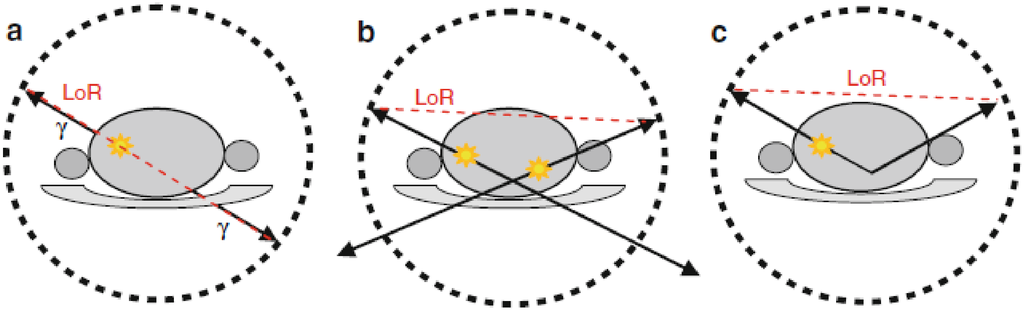


Figure 2.2 Coincidence events in PET **(a)** A true event, **(b)** a random event, **(c)** a scattered event[27]

In the past few years, PET/CT systems with time of flight (TOF) capabilities have become commercially available. TOF is based on the difference in arrival or detection time of both 511keV annihilation photons when the annihilation took place at off-axis locations. The difference in detection time contains information about the position of the positron emission along the LOR. TOF requires a high timing accuracy and fast detectors with high sensitivity and fast electronics. [24–28]

Other corrections need to be applied during the reconstruction process to increase the accuracy of the final image. Some of these corrections include dead time corrections to deal with the high-count rates found in PET. However, the most important of the corrections applied in PET is that to correct for photon attenuation. Both photons need to be detected for a signal to be registered; this means that the full thickness of patient tissue traversed by both photons affects the relative attenuation of signal from different parts of the patients. At the present, CT is the attenuation correction (AC) method of choice. CT-AC brings a lot of advantages such as practical and effective approach of acquiring co-registered anatomical and functional images in a single scanning session and increase of both sensitivity and specificity. Exact AC is relatively straightforward, using an effectively map of attenuation at X-ray energies, with appropriated conversion factors, provide AC map in a matter of seconds.[24,27]

PET/CT examinations are most carried out using a low-dose CT technique, which is often labelled ‘non-diagnostic’.[24,28]

2.2.2 Image Quality

When compared to other imaging modalities PET exams are limited by their low spatial resolution and signal-to-noise ratio (SNR). However, there is always an interest in decreasing as much as possible the administrated activity, for patient and staff safety and economic reasons without compromising the level of diagnostic accuracy.[24,25]

In PET the assessment of IQ can be challenging because this task is affected by two different variables, biological and physical/technological factors.

Table 2.3 demonstrate how biological factors can decrease IQ.

Table 2.3 - Influence of biological factors in IQ

Factor	Description
Weight /BMI composition	Body fat will increase attenuation factors and consequently IQ will decrease, compromising diagnoses. One of the methods to prevent this is increasing administrated activity (however this is restricted until a maximum amount due to International Commission on Radiological Protection (ICRP) limits.) or scanning time (which can lead to movement during acquisition due to longer scans and uncomfortable positioning). More information in 2.2.3[29–31]
Post injection uptake	European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine and Molecular Imaging (SNMMI) propose an optimal time interval to achieve the best SNR and consequently IQ. Longest post injection acquisition will be led to decrease in IQ and sometimes scanning time needs to be increase.
Respiratory motion	Breathing during PET vs CT may lead to incorrect AC and bias in quantitative parameters, masking of underlying organ activity, that can influence the final diagnose.[31]
Movement during acquisition	Movement during acquisition will interfere in the reconstruction processes and alignment between CT and PET that can lead to miss interpretation or lack of IQ.[31]
Co-morbilites	Sometimes patients have extra needs associate with or not, with the clinical indication to perform the scan. One of the most common co-morbilites is a catheter in situ which will fill up during the scan changing the count rate around the area where it is place. Another example is tremors associated with Parkinson which will prevent the patient from lying still during acquisition. All this factor will influence the final image, and sometime extra pictures are performed to ensure IQ.

In the table 2.4 physical and technological parameters will be described and how they can impact the IQ.

Table 2.4 – Influence of physical and technological parameters in IQ

Factor	Description
Sensitivity	Sensitivity is described as number of counts detected per unit of time per unit of radioactive concentration present in a source. It is influenced by time of decay, density, and thickness of the material. It might be improved by increasing the number of rings in the system, however, will always decrease from the centre to the periphery.[3233]
Reconstruction parameter changes	Reconstruction parameters such as matrix size, FOV, and TOF reconstruction could substantially change quantitative parameters for small lesions.[24,32]
Calibration error between scanner and dose calibrator and timing mismatch	Improper calibration between scanner and dose calibrator can result in errors in quantitative parameters, being this error more relevant in small lesions. Error in calculation of decay time between injection and scanning time, for example because the correct decay spreadsheet was not use, will affect calculated quantitative parameters; studies have revealed a linearly dependent on the timing error and quantitative parameters calculation.[24,32]
Partial volume Effect	The partial volume effect (PVE) is where parts of the image are blurred due to a of signal between adjacent regions. The PVE affects small focal regions of tracer uptake and the edges of regions of larger uptake.[33]
Radionuclide	Positron physics ^{68}Ga has a lower positron yield than ^{18}F (89.14% and 96.86% respectively). The detection sensitivity has been measured to be up to 15% lower for ^{68}Ga. The single photon emission in the 350 – 650 keV range (0.034%), and scattered photons from high energy emissions (3.451%) can increase noise within ^{68}Ga PET images.[5]

2.2.3 Weight versus BMI in imaging quality.

The BMI is the metric currently in use for defining anthropometric height/weight characteristics in adults and for classifying (categorizing) them into groups. The common interpretation is that it represents an index of an individual fatness.[34]

BMI considers natural variations in body shape, giving a healthy weight range for a particular height.[35]

Table 2.5 express the World Health Organization (WHO) classification for BMI values.

Table 2.5 BMI categories according to WHO Fonte: https://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi

BMI	**Classification**
<18.5	Underweight
>18.5 – < 24.9	Normal
>25 - <29.9	Overweight
>30 - < 34.9	Obese- Class I
>35 - < 39.9	Obese – Class II
>40	Obese – Class III

Obesity is currently one of the most important public health problems in developed countries representing a serious medical, social, and psychologic reverberations, affecting virtually all ages and socioeconomics groups. Imaging obese patients presents several challenges to technologists acquiring the images and the physicians interpreting them.[29–31]

In cancer patients, the therapeutic options and prognosis strongly depend on accurate imaging that encompasses the entire body.[31]

The most challenging aspect of imaging obese patients is ensuring that the entire anatomy can be visualized and radiation in CT can be limited by inadequate penetration. Obese patients have higher photon attenuation and scatter fraction turning IQ suboptimal during PET / CT acquisition when comparing with normal weight patients.[29,31]

To compensate for the increased weight, some centres advocated that the injected activity or acquisition time must be adjusted, however both solutions have some restrictions. However, the radiation dose to the patient recommended by the ICRP limits the increase in activity, and hence the dose may not be high enough to produce an adequate study for proper interpretation due to reduced SNR and increased scatter in the acquire image. Increasing the administrated activity may raise the dead time and consequently decrease IQ.[29–31]

On the other hand, increasing scanning time can be difficult to implement because that would mean less patients scanned per day and more time under the scanner which could be difficult in patients with increase body habitus added to other co-morbidities which will lead to movement during the acquisition, as an example, it has been suggested that patients weighting 120 kilos (kg) need a PET acquisition 2.3 times longer than that for a 60 kg person to obtain the same SNR.[28–30]

The problems previously mention show how that the patient weight is a limiting factor for dose adjustment and more medical expertise thinks using weight for dose adjustment is an obsolete criterion, that is why news studies have suggested a new approach, instead of using the weight as the main characteristics using BMI for administrated calculations. (No studies have been performed to access how increased BMI patients will affect ^{68}Ga-DOTA-SSA PET / CT will be affect so all this literature will be base in studies using ^{18}F-FDG PET / CT).[29,31]

Sanchez-Jurado et al. performed a study where they recruited 1.000 patients which were administrated according to the old regime based on weight and 800 patients were enrolled in this study and injected with the new regime based on BMI. For the weight based a bolus of ^{18}F-FDG injection of 5.55-7.4 MBq/kg was administrated and 6.85-11.1 MBq/BMI to the experimental group.[29]

All the patients were IQ scored according to the dose calculations criteria. When comparing the scoring results by subgroups, the same IQ results were obtained in underweight and morbidly obese patients however better results were achieved in normal-weight, overweight and obese patients. These can prove that BMI method works better than the body weight-derived method.[29]

One example of it, is figure 2.3, where patients with the same weight, using the old methods would be injected with the same amount, though using BMI method is easy to understand that higher BMI leads to more activity administrated without compromising image quality. [29]

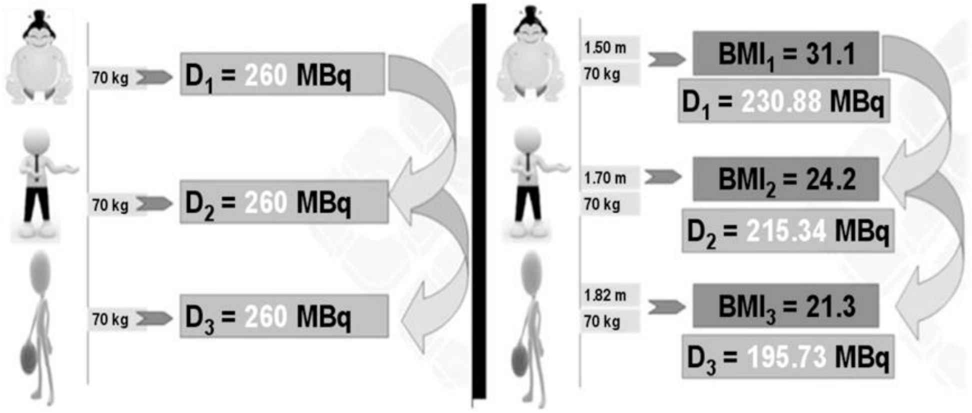


Figure 2.3 (Left) ^{18}F-FDG doses administrated to 3 patients with the same weight according to current international guidelines (right) ^{18}F-FDG doses adjusted based on BMI.[29]

2.3 PET/CT – ^{68}Ga-Somotostatin Analogues

2.3.1 Characteristics of ^{68}Ga

^{68}Ga has a short half-life of 67.71 min with a high positron emission fraction (89%) maximum energy of 1899 keV and mean energy of 890 keV which provide sufficient levels of radioactivity for high IQ while minimizing radiation dose to the patient and staff, allowing short scanning times and repetitive examinations.[27,28]

^{68}Ga can be produced from cyclotron or from Germanium-68 (^{68}Ge)/^{68}Ga generators, which constitute enrichment to NM departments without cyclotron nearby. When compared to cyclotron, ^{68}Ge/^{68}Ga generators bring some advantages such as it does not require special premises with radiation shielding constructions, consumption of energy and highly qualified staff for running and maintaining the equipment. However even with these qualities not every NM facility is equipped with these generators, being this produce limited to large departments/hospitals.[36]

^{68}Ga generators producers are an attractive isotope for PET imaging not only because of the 271-day half-life of the parent ^{68}Ge meaning that generators can be used for approximately 1 year, but they are also highly reproductible and straightforward chemistry.[24,27]

2.3.2 ^{68}Ga-DOTA-SSA – Characterization

The introduction of SSA labelled with the positron-emission radionuclide ^{68}Ga for PET/CT was possible by the development of 1,4,7,10-tetraazacyclododecane-1,4,7,10-

DOTA, a macrocyclic chelator capable of forming stable complexes with charged radiometals, which will be coupled with the SSA, chemical structure shown in figure 2.4.[19,21,22]

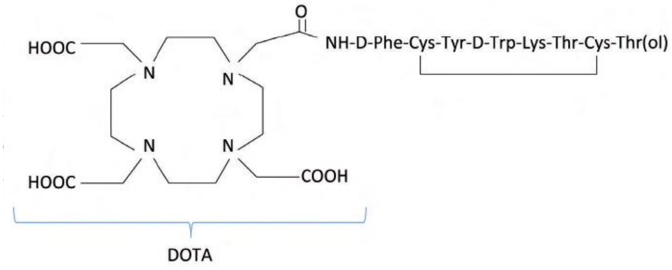


Figure 2.4 Chemical structure of ^{68}Ga-DOTA-Tyr^{3}-octreotide. The macrocyclic chelator DOTA is conjugated with the octreotide SST analogue and this complex is labelled with ^{68}Ga[25]

There is currently a wide variety of automatic models for the synthesis of this radiopharmaceutical, with the most diverse radiochemical strategies and reagents to produce DOTA-SSA, however no automatic model is approved by the Food and Drugs Administration (FDA) or the European Medicines Agency (EMA) due to the multiple phases of the process, which can lead to several sources of error and production failure.[36,37]

That is why Advanced Acellerator Apllication (AAA) has developed two new 'ready-to-use' kits, the SomaKIT TOC® approved for use in Europe and in the USA and the NETSPOT® approved only in the USA, reducing the number of steps associated with labelling and synthesis time.[36,37]

The SSA mostly used in clinical setting are DOTANOC, DOTATOC and DOTATATE having different affinities for SSTRs. All SSA mentioned can be linked to SSTRs 2 showing higher affinity than ^{111}In-DTPA-octreotide, however they have different affinity profiles for other SSTRs, particularizing DOTANOC also has high affinity for SSTR5 and to a lesser extent for SSTR3, while DOTATOC shows some affinity towards SSTR5. Nevertheless, the affinity of DOTATATE for $^{\text{SSTR2}}$ is an order of magnitude higher than that of the other DOTA-peptides.[19,21]

Recent studies, always using the same patients, but varying the SSTRs administered, have shown that DOTATOC can detect more injuries, with Standard Uptake Values (SUV) higher than DOTATATE. However, when DOTATATE is compared to DOTANOC demonstrates higher SUV values[38]

A meta-analysis regarding the diagnostic role of ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE reported a high sensitivity (93% and 96% respectively) and specificity (85%

and 100% respectively) for both tracers.[38,39] Currently there is no recommendation on which ^{68}Ga-DOTA-SSA is preferred but head-to-head comparison studies have been performed. In one of this comparison studies between ^{68}Ga-DOTATATE and ^{68}Ga-DOTANOC in 20 NET patients, a comparable diagnostic accuracy was found however ^{68}Ga-DOTATATE was capable of detecting more lesions sites (130 vs 116), however this difference was considered not statically significant.[21,38] In a similar head-to -head comparison of ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE in 40 NET patients showed comparable diagnostic accuracy, although significantly fewer lesions were detected with the latter (262 vs 254).[38,39]

2.3.3 68Ga-DOTA-SSA PET/CT Guidelines

The primary indication for ^{68}Ga-DOTA-SSA PET/CT is for imaging of NETs which usually express a high density of SSTRs to localize primary tumours and detect sites of metastatic diseases, follow up patients with known disease to detect residual, recurrent or progressive disease (re-staging) and select patients with metastatic disease for PRRT.3,4,40

For a ^{68}Ga-DOTA-SSA PET/CT to be performed, an assumption must be verified, so therapies with short-term and long-term SSA should be discontinued 24h and 3-4 weeks respectively so that the SSTRs are not blocked.[3,4,20]

Depending on the SSA used different activities can be administrated, ranging for 100 - 200 MBq for DOTATOC and 2MBq/kg for DOTATATE. (more information can be found on chapter 2.3.5 – Protocol Limitations). [3,36,38,40]

Patients should be encouraged to drink enough water before and after tracer administration to increase IQ in the abdomen. Before scanning starts patients should void to reduce the background noise and this process should be repeat frequently during the day to decrease the radiation dose to the excretion organs.[3,4]

Images are acquired 45-60 min. after administration, from the vortex to the head of the femur with an average duration of 25 min., always accompanied by a CT scan to correct the attenuation and better anatomical location. The biodistribution of ^{68}Ga-DOTA-SSA is shown in figure 2.5. Physiologic uptake is high in SSTR 2-rich organs such as the pituitary gland, spleen, adrenals, liver, pelvicalyceal system of the kidneys, and urinary bladder. Lower uptake ay physiologically observed in the thyroid, pancreatic head, stomach, small and large bowel, and prostate.[4,20,27,38]

Compared with ^{18}F-FDG PET/CT, there is minimal background activity in soft tissue and muscle, which contributes to high tumour-to background contrast at pathologic sites.

The uptake also contributes to a ‘sink effect’, whereby physiologic uptake, particularly in the spleen and liver is reduced in patients with high burden disease. Uptake at pathologic and physiologic sites may change in patients who undergo concomitant short or long-acting SSA therapy, which competes with the radiotracer for bioavailability.[3,4,20]

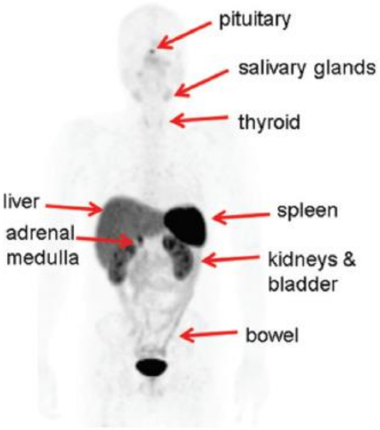


Figure 2.5- ^{68}Ga-DOTA-SSA PET Normal Biodistribution[3]

The highest absorbed doses are observed in the spleen and urinary bladder wall, followed by the kidneys, adrenals, and liver. The effective radiation dose resulting from the administration of 185MBq to an adult weighting 75 kg is about 4.8 millisieverts(mSv). For this activity, the typical radiation dose to critical organs, which are the urinary bladder wall, the spleen and the kidneys are about 0.125, 0.282 and 0.0921 mSv/MBq, respectively. Since the spleen has the highest physiologic uptake, higher uptake, and dose to normal or tumour tissue may occur in patients with splenectomy as demonstrates for ^{68}Ga-DOTATOC.The effective dose deriving from the low-dose CT component in generally in the range of 9mSv for 80 milliamperes (mA).[3,4,20]

2.3.4 Protocol Limitations

According to the guidelines of the EANM, for the realization of a ^{68}Ga-DOTA-SSA PET / CT, the administered activity should be between 100-200 MBq, considering the quality of the PET equipment, but without ever considering the weight, height or BMI of the patient.[4]

The lack of a dose regimen causes some problems, imagine two patients who were administered with the same activity, however one of the patients is 50 kg and the other 90 kg. It will be expected that the images of the first patient will present a better quality due to the lesser attenuation of radiation by the adipose tissue. On the other hand, the

ALARA principle may not have been fulfilled since the 50 kg patient may have been administered with an activity greater than that required to obtain an image with diagnostic value. [3,4]

More recently, in 2017, these same guidelines were revised for ^{68}Ga-DOTATATE, and an administration of 2MBq / kg was set, maintaining the minimum and maximum limit with the same values, and suggesting that a patient weighing 75kg should be administered with 185MBq. [20]

However, for ^{68}Ga-DOTATOC the activities to be administered are not in agreement between FDA and EMA. In April 2020, the guidelines established by the EMA stated that for a 70kg patient, 100-200MBq should be administered, stressing that this value could be adjusted to the patient's characteristics, but never offering a dose regimen. On the other hand, the FDA approved the somaKIT® in 2019, stating that the activity to be administered to an adult should be 148MBq, assuming an interval between 111MBq and 185 MBq.[37]

No studies were performed using BMI to achieve a dose regime for ^{68}Ga-DOTATOC-PET / CT.

Chapter III- Participants and Method

3.1 Study Characterization

This is an observational retrospective study that focuses on a sample which realized a ^{68}Ga-DOTATOC PET/CT scan between 5th of March 2020 and 31st of July 2020, at the NM department at University Hospital of Coventry and Warwickshire (UHCW).

3.2 Sample

All the patients included in this study have had a ^{68}Ga-DOTATOC PET/CT. To achieve the objectives explained previously, after analysing the entire sample, this one was divided in different groups according to the IQ score. IQ score was divided in 4 categories: Non-diagnostic (ND), Poor (P), Moderate (M) and Good (G).

3.3 Inclusion and Exclusion Criteria

Inclusion criteria were defined as:

- Patients older than 18 years
- Patients where pharmacological therapy is not having the desired effects.
- Performing the ^{68}Ga-DOTATOC exam, 4 weeks after therapy with long-term cold somatostatin analogues and 24 h after therapy with short-term somatostatin analogues.
- Whenever possible, perform the ^{68}Ga-DOTATOC exam as close as possible to the next pharmacological therapy.

Exclusion criteria were defined as:

- No authorization from patient to use the data for scientific purposes.
- Women who were breastfeeding or pregnant
- Injection extravasation

3.4 Methodology

The methodology which will be explained is based on the NM department protocol at UHCW for ^{68}Ga-DOTATOC PET/CT.

The following explanation will be divided in four subtopics, scheduling ^{68}Ga-DOTATOC PET/CT, preparation for the ^{68}Ga-DOTATOC PET/CT, administration and uptake time and acquisition protocol.

- *Scheduling ^{68}Ga-DOTATOC PET/CT.*

Each patient received a letter with the appointment time and date and a brief explanation of the procedure. Furthermore, the radiopharmacy manager contacted every single patient to make sure all the requires would be meet, such as no long-active SST therapy for at least 3 - 4weeks and no short-active SST therapy for at least 24h. Another question asked was if there was any date for the next cycle of therapy, that way the scan could be performed as close as to this date according to the department availability.

In this phone call the technologist also explained how long the procedure would take, advise patient to bring comfortable and non-metal clothes and answer any concerns that the patient would have.

- *Preparation for the ^{68}Ga-DOTATOC PET/CT*

On the day of the scan, one of the NM assistants or NM technologists prepared the patient for the scan, starting to measure the height and weight to SUV calculations purposes.

After that, a brief explanation of the procedure was given to the patient, emphasised the importance of keeping a distance from pregnant ladies and small children until the end of the day and how hydration plays a key part of flushing the radiation quicker from the body, reducing the exposure to critical organs. Was also allowed time for the patient to raise any concerns or ask any question.

The next step taken was the placement of a 22 G cannula or a 24G cannula in patients with poor venous access. These cannulas were placed to minimise the exposure to the technologist while injecting and assuring the administration on the correct time, reducing the possibility of extravasation.

Informed consent was acquired at the time of the examination, when preparing the patient for the procedure (see appendix II). This same informed consent was signed by the patient specifying the date.

When all the above procedures were completed the NM staff took the patient to the bed bay area where one bed was assigned to the patient. This room was at environment temperature around 24º Celsius (ºC); however, a blanket was offer to every patient. If the patient arrived with any metal on their clothes, one gown would be provided and a basket to place their belongings.

- *Administration and uptake time*

The injection was performed with the patient lie down and the cannula was removed 10 min after injection by another member of staff.

Patients waited between 40-60 min to start the scan.

- *Acquisition protocol*

Before starting the scan, patients were instructed to go to the toilet to void the bladder for comfort purposes and ease of application of reconstruction e correction algorithms.

^{68}Ga-DOTATOC PET/CT initiated with the acquisition of a topogram, which is used to establish acquisition limits.

Then a low dose CT is acquired followed by the PET acquisition. All the acquisition parameters are illustrated in table 3.1.

Table 3.1 Acquisition parameters for ^{68}Ga-DOTATOC PET/CT

PET/CT Acquisition Parameters	
CT	
Tube Voltage (kV)	120
Tube Current (mAs)	70
Number of slices	64
Rotation Time (second/rotation)	0.35
FOV (mm)	15.7
PET	
Time per bed (min)	3
Total acquisition time	24 (8 beds) / 27 (9 beds) From vortex (skull base) to inguinal region
Positioning	Supine, arms above the head (when possible), otherwise arms along the side
Matrix (pixels)	128 x 128
Reconstruction algorithms	Iterative – Q-clear
Co-registration	Axial, Sagittal and Coronal

To ensure a better CT dose distribution, patient positioning (as close as possible to the centre of the FOV) and starting point of acquisition lasers were used. External lasers were selected and marked in the vortex of head.

All the relevant information regarding individual characteristics of the patient or the scan were register in the appropriate Ionizing Radiation Medical Exposure Regulations (IRMER) (see appendix III).

After acquisition images were reconstructed and sent to Picture Archiving and Communication System (PACS).

BMI values for each individual patient were calculated using the equation 3.1.

Equation 3.1 Equation for BMI calculus

$$\mathbf{BMI} = \frac{\mathbf{Weight}\ (\mathbf{Kg})}{\mathbf{Height}^{\mathbf{2}}(\mathbf{m})}$$

On the other hand, Interval Time was calculated follow equation 3.2:

Equation 3.2 Equation for Time interval calculus

$$\mathbf{Time\ interval(\ min) = Time\ of\ scan - Time\ of\ injection}$$

3.5 Equipment

Patient acquisitions were performed on a General Electric (GE) Discovery PET/CT 710 scanner, figure 3.1. The Discovery PET/CT 710 uses lutetium-based scintillation crystals, allowing TOF capability.[41]

PET subsystem is equipped with 13824 crystals with a size of 4.2 x 6.3 x 25 millimetres per cube (mm^3). [41]

System sensitivity is 7.0 counts per seconds (cps)/ kiloBequerel (kBq) with a scatter fraction of 37%.[41]

Physical parameters are 70 cm and 170 cm for patient por diameter and patient scan range, respectively.[41]

Figure 3.1 GE Discovery PET/CT scanner *reference*: https://www.oncologysystems.com/inventory/medical-equipment-for-sale/used-petct-scanners/ge-discovery-710-128-slice-pet-ct-scanners

3.6 Variable Definition

Table 3.2 presents all the variable included in this study. All the variables are classified according to statistics rules and a brief description is available.

Table 3.2 Variables Characterization

Qualitative Nominal Variables	
Variables	**Characterization**
Gender	Woman and Man
Primary tumour	Appendix; Glomus Jugular; Lung; Ovary; Pancreas; Parathyroid; Rectum; Stomach; Small Intestine; Thymus; Thyroid; Unknown
Qualitative Ordinal variable	
IQ score	**1 -** Non- diagnostic; **2 -** Poor; **3 -** Moderate ;**4 -** Good
Quantitative Continuous Variables	
Activity	MegaBequerel
Activity/BMI	MegaBequerel per Body Mass Index (see equation 3.4)
Activity/weight	MegaBequerel per Kilogram (see equation 3.3)
Age	Years
BMI	Without scale (See equation 3.1)
Height	metres
Time of injection	minutes
Time of scan	minutes
Weight	kilograms
Quantitative Ordinal Variable	
Time interval	minutes (see equation 3.2)

Variables that were calculated to help developing this project were Activity/weight and Activity/BMI. Each one of them were calculated using equation 3.3 and equation 3.4 respectively:

Equation 3.3 Activity/weight formula

$$\mathbf{Activity/Weight}(\mathbf{MBq/Kg}) = \frac{\mathbf{Activity\ (MBq)}}{\mathbf{Weight\ (Kg)}}$$

Equation 3.4 Activity/BMI formula

$$\mathbf{Activity/BMI} = \frac{\mathbf{Activity\ (MBq)}}{\mathbf{BMI}}$$

To perform IQ 2 technologists with more than 5 years of experience were asked to assess each image randomly from PACS. No information regarding weight, height or BMI was provided.

Both technologists assessed the images in one day without any breaks and without anyone in the room.

Each technologist scored all images subjectively for visual diagnostic IQ using the four-point scoring scale from *Halpern et al. (2005)* [42] ND (1), P (2), M (3), G (4).

3.7 Statistical Analyses

The first analysis performed was a descriptive one, where it was analysed the distribution of the sample according to diverse parameters such as age, weight, height, BMI, activity administrated, time of interval or primary site of NET. This step was completed also for the same variables but when divided by the 4 IQ scores.

Subsequently, all the quantitative continuous variable were subjected to statistical tests (results can be seen in chapter 4).

A 95% interval of confidence was considered.

All statistical analyses were performed using IBM SPPS statistics version 24.

3.8 Ethical Considerations

This project was approved by the Head of the NM Department, James Cullis on the behalf of the UHCW (see appendix I).

Informed consent was acquired at the time of the examination; when preparing patient for the procedure (see appendix II to the example of consent used at the UHCW)

The same project was subjected for approval by the Ethic Commission of Escola Superior de Tecnologia da Saúde de Lisboa, receiving a positive response on the 7 of July 2020. (appendix IV).

All data was anonymized and codified to ensure that anonymize and confidentiality principle was followed. There is no conflict of interest, and this project was realized without any kind of financial benefit.

Chapter IV- Results

A total of 82 patients were included, 41 men (50%) and 41 women (50%). Subject characteristics and the measurements/ calculations of the patient-dependent parameters are summarised in Table 4.1, where time interval is characterized as the interval between injection and scanning acquisition.

Table 4.1 Characteristics of subjects and patient dependent parameters

Parameters	Mean ± SD	Range
Age(year)	63.12 ±13.24	21-82
Weight(kg)	80.88 ±17.40	43.5-129.0
Height (m)	1.67 ±0.09	1.48-1.85
BMI	28.92 ±6.34	18.34-54.39
Activity (MBq)	166.76 ±16.16	94-202
Time Interval (min)	54.30 ±10.03	40-91
Act/BMI (MBq/BMI)	6.01 ±1.33	2.83-10.09
Act/Weight (MBq/kg)	2.16 ±0.52	1.19-4.25

SD: Standard Deviation

The descriptive analysis focusing on the primary site of tumour for the population in study is showed in figure 4.1.

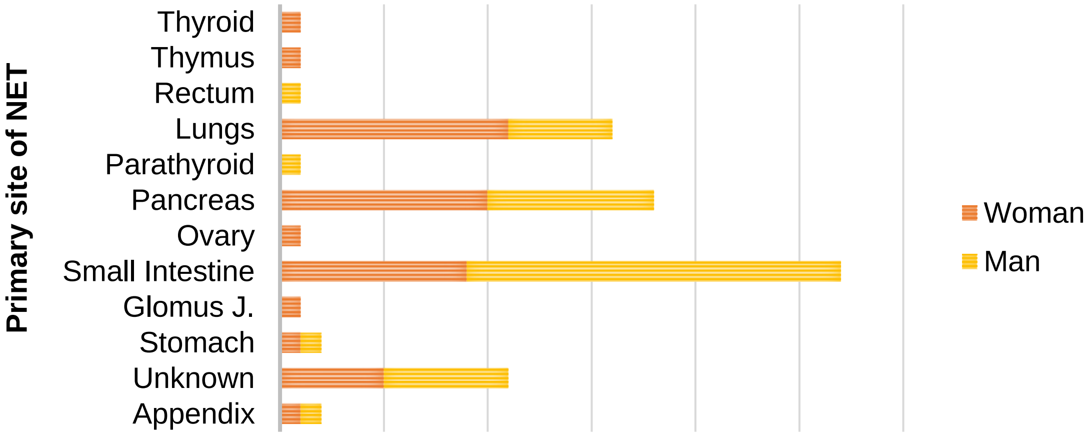


Figure 4.1 Primary site of NET according to patients' gender

In this sample small intestine was classified as the most common primary site of NET for men and lungs for women, which is in line with the literature, that describe GI and respiratory tract as the most common place for primary. It is also important to mention that 11 patients (5 women and 6 men) which constitutes almost 10% of this sample are classified as unknown for primary site of NET.

When analysing the BMI distribution of this sample according to the gender, using a circular graph (figure 4.2), it is possible to see that both genders have more patients classified as overweight, 42% for women and 39% for men. On the other hand, the underweight group reflects the group with lower cases, 2% for women and 0% for men.

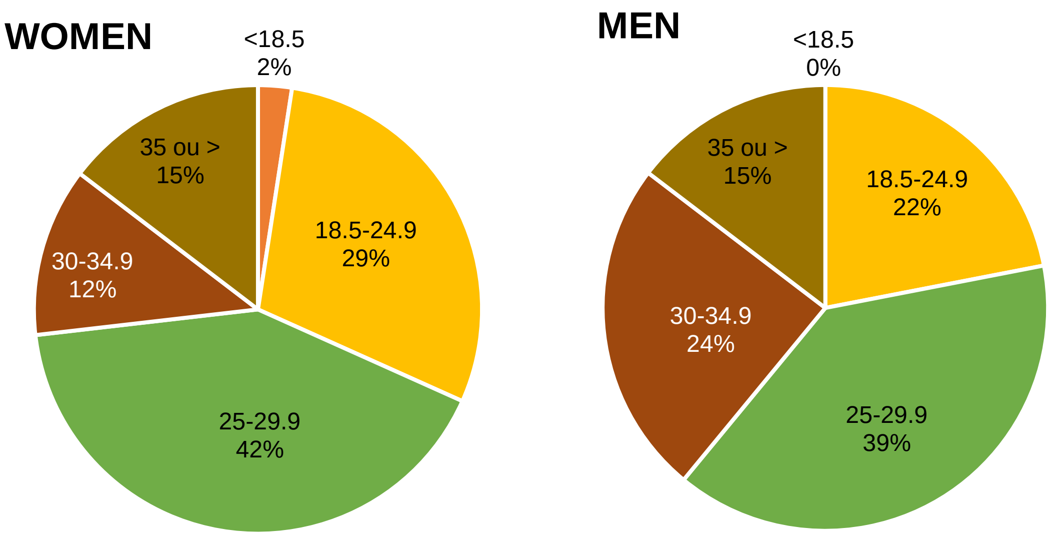


Figure 4.2 BMI sample distribution according to gender

Normality test using Kolmogorov-Smirnov-with Lilliefors Correction where applied where only Activity/weight, Activity/BMI and height were classified as normal (with a p value of 0.200 for activity/weight and activity/BMI and 0.173 for height). The other 3 variable achieved p values of 0.011 (weight), 0.004 (BMI), 0.009 (activity).

Scatter plots were obtained to access how the different variables in study would correlationate between themselves, results are shown in figure 4.3. Like expected there is almost no correlation between the weight or BMI and the administrated activity. This is due to no dose regimen implementation at the time of the study, so every patient received between 100-200MBq not having in consideration biological factors that can affect IQ.

When perform scatter plots to access weight versus activity/weight or BMI versus activity/BMI it is possible to see a correlation between these factors where lower weight/BMI would have received higher activity. This was the starting point that lead to the construction of a dose regime.

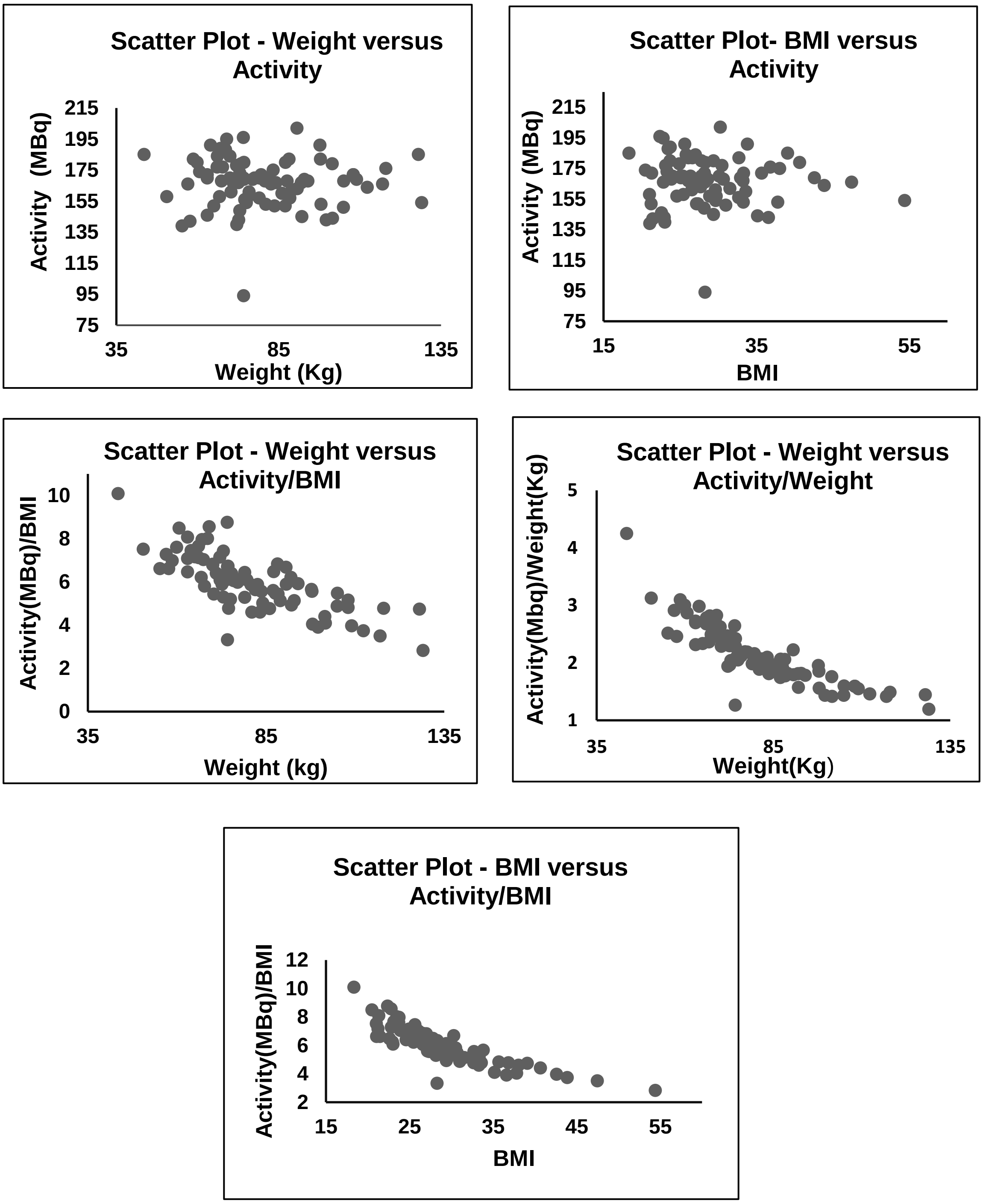


Figure 4.3 Scatter plots for comparison between different variables

IQ score was performed by two independent observers and the number of patients in each category for each observer are in table 4.2. Can be visualized that IQ score poor was the category where the number of patients differ the less (25 patients for observer 1 against 24 patients for observer 2).

ND score is not represented in table 4.2 due to the same patient have been selected. It is important to mention that the patient in the ND might have had an injection extravasation – this cannot be confirmed because the injection site was out of the FOV, however all the other parameters that can influence the IQ were in line with the UHCW protocol and patient BMI was considered normal. That why ND was not use in the following analysis.

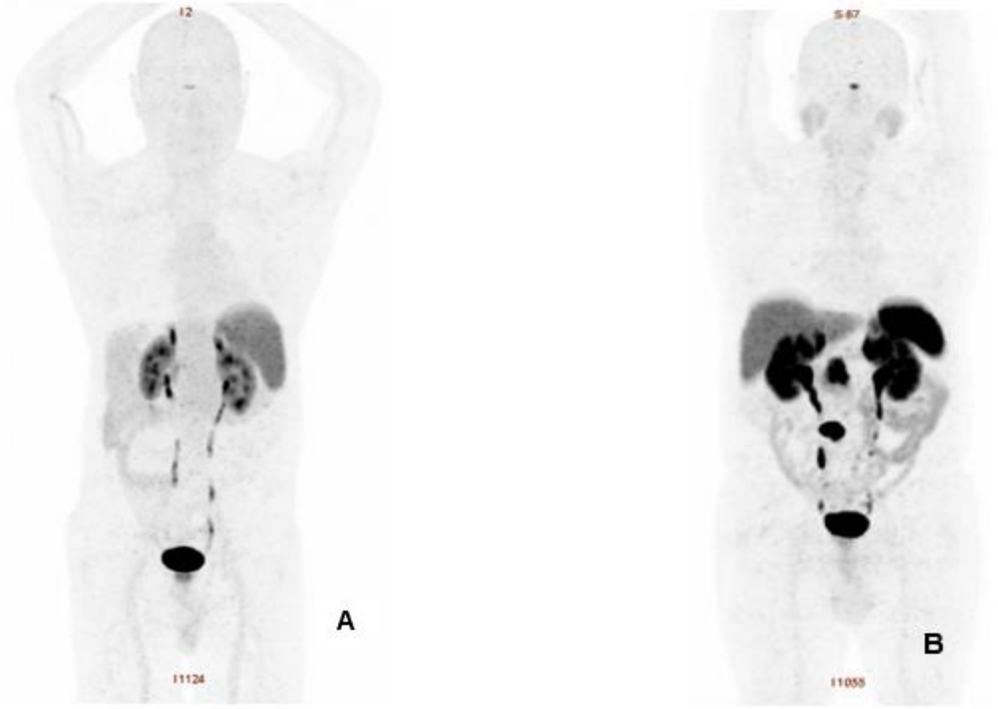
Table 4.2 Number of patients per IQ score.

Pet IQ	**Poor (2)**		**Moderate(3)**		**Good (4)**	
	Observer		**Observer**		**Observer**	
	1	**2**	**1**	**2**	**1**	**2**
Number of patients	25	24	30	38	26	19

Some examples of ^{68}Ga-DOTATOC PET – CT scans are shown in figure 4.4 and 4.5 and patients characteristics can be found in table 4.3.

Table 4.3 Patient's characteristics for figure 4.4 and 4.5.

Patient	**Weight (kg)**	**BMI**	**Activity (MBq)**	**Time interval (min)**	**IQ Score**
(A)	72	23	140	58	4
(B)	75	26	167	77	3
(C)	86	33	168	60	3
(D)	100	36	143	45	2
(E)	117	47	166	42	2
(F)	129	54	154	72	2

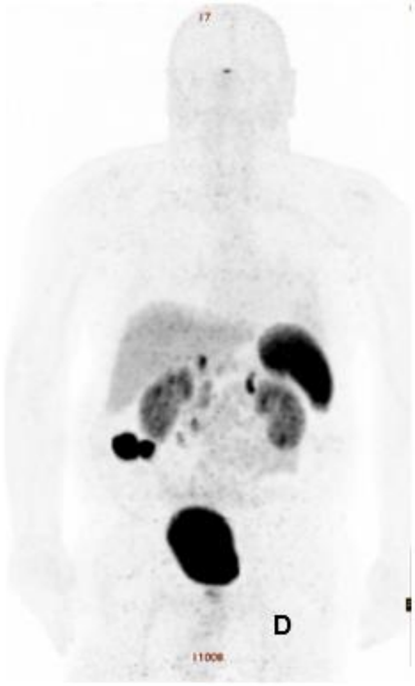


BMI= 23 (NORMAL)

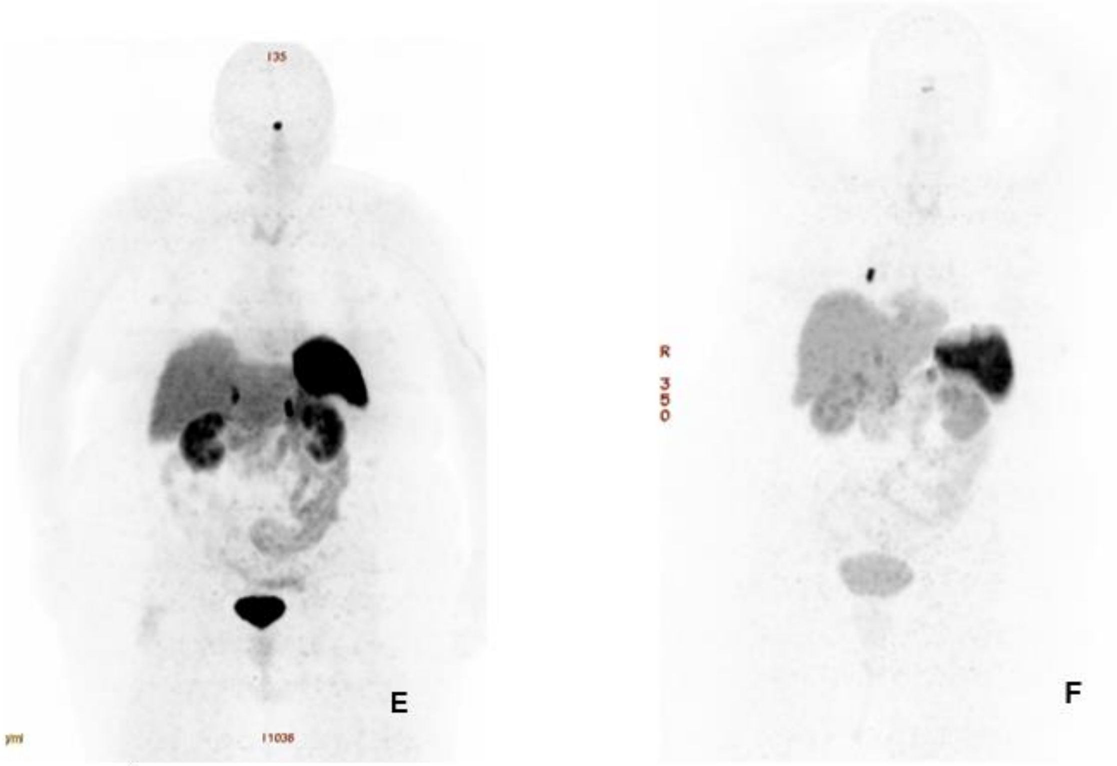
BMI = 26 (OVERWEIGHT)

BMI = 33 (OBESE CLASS I)

Figure 4.4 (A) Patient with BMI 23 – IQ score 4 – G**; (B)** Patient with BMI 26 - IQ score 3 – M;
(C) Patient with BMI 33 IQ score 3 - M



BMI = 36 (OBESE CLASS II)



BMI: 47 OBESE CLASS III

BMI: 54 OBESE CLASS III

Figure 4.5 (D) patient with BMI 36 IQ score 2 - P; **(E)** patient with BMI 47 IQ score 2 – P; **(F)** patient with BMI 54 IQ score 2 - P

More information about patients which were classified differently by the observers can be found in table 4.4. Figure 46 provide some visual examples of that patients.

Table 4.4 Patient's parameters where observers had different IQ scores.

Parameters					**Observer (IQ score)**	
Patients	**Weight (kg)**	**BMI**	**Activity (MBq)**	**Time Interval (min)**	**1**	**2**
24	72.7	22.94	143	45	4	3
27	68.6	23.46	188	72	4	3
33	58.7	26.09	182	66	4	3
35	66.1	25.82	184	62	4	3
38	64	25.64	191	44	4	3
48	75.3	24.59	157	54	4	3
50	63	21.30	172	45	4	3
55	105	30.68	168	45	3	2
56	74.2	25.38	170	53	3	4
68	74.5	32.67	156	58	4	3
75	75	29.67	157	67	2	3
78	87	27.15	152	47	2	3

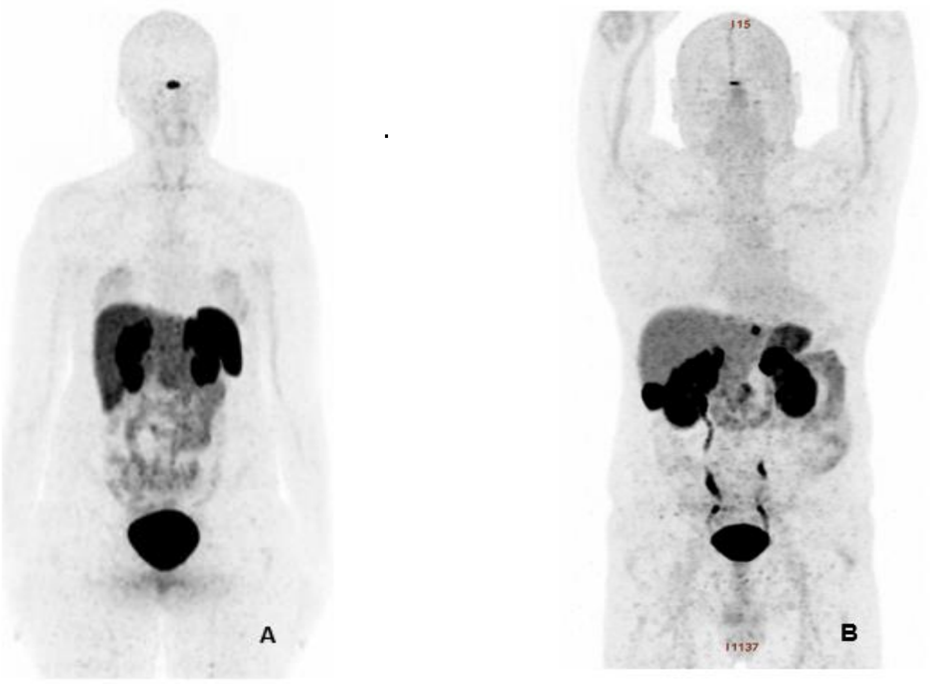


Figure 4.6 (A) patient number 24**; (B)** patient number 55 – patients which received different IQ scores from observer 1 and 2.

Normality tests were also tested for weight, height, BMI, activity, activity/weight, and activity/BMI but this time they were divided according to the IQ score. This test was performed for observer 1 and 2. For this test Shapiro Wilko- with Lilliefors correction were used because each sample had less than 50 individuals.

For both observers activity/BMI was the only variable classified normal in all 3 IQ scores.

Nevertheless, observer 1 also had variable weight classified as normal for all 3 scores.

With this information statistic tests were applied to confirm if there was any significant difference in the mean Actvity/BMI between IQ scores for both observers. First levene test were applied to evaluate the homoscedastic of the sample (if they had equal variance). Because this criterion was achieved in all comparisons unpaired T-test- with Welsh corrections was apply with a α of 5%. The results showed that the mean Activity/BMI is significantly different between all the groups and in both observers, table 4.5.

Table 4.5 T Test for comparison IQ score groups

Comparison groups	**T Test (α=0.05)**	
	Observer 1	**Observer 2**
IQ (4) – IQ (3)	<0.001	<0.001
IQ (4) – IQ (2)	0.000	0.000
IQ (3) – IQ (2)	0.007	0.001

Overall interobserver agreement was verified by applying Fleiss Kapp tests. The same test was performed to access the interobserver agreement between the difference IQ scores.

Fleiss Kappa achieved a result of 0.779 meaning that there is substantial agreement between observer 1 and 2.

Table 4.6 shows a more detailed interobserver agreement when comparing IQ scores separately. Analysing it, it is easy to conclude that poor IQ score have an almost perfect agreement, which corroborate table 4.2 where there just a patient difference (observer 1 - 25 patients and observer 2 – 24 patients).

With regard, M and G IQ score both are classified as a substantial agreement between observers.

Table 4.6 Interobserver agreement by IQ score groups.

Group	ICC	95% CI
Poor (2)	0.913	0.906-0.920
Moderate (3)	0.699	0.692-0.705
Good (4)	0.724	0.717-0.731

ICC – intraclass coefficient

CI- confidence interval

Table 4.7 demonstrates patients' characteristics in each IQ score for observers.

Table 4.7 Patient's characteristics in each IQ score for observer 1 and observer 2

Pet IQ (Mean ± SD)	Poor		Moderate		Good	
	Observer		Observer		Observer	
	1	2	1	2	1	2
Weight (kg)	95.24± 15.14	96.84± 14.82	82.16± 14.08	78.70± 13.42	66.38± 9.36	66.17± 10.50
Height (m)	1.68± 0.10	1.68± 0.11	1.69± 0.08	1.67± 0.08	1.66± 0.09	1.66± 0.83
BMI	34.20± 6.68	34.53± 6.63	28.88± 4.56	28.15± 4.52	24.23± 3.11	23.84± 2.89
Activity (MBq)	166.48± 13.62	167.67± 13.28	163.17± 16.68	161.11± 17.19	170.88± 17.61	170.53± 17.58
Time interval (min)	56.60± 11.46	56.08± 11.57	54.67± 8.97	55.32± 9.34	51.81± 9.71	50.21± 8.82
Activity /BMI (MBq/BMI)	5.03± 0.98	5.02± 0.99	5.78 ± 0.95	5.96± 1.07	7.14± 1.07	7.23± 1.05
Activity/Weight (MBq/kg)	1.79± 0.31	1.77± 0.31	2.03± 0.35	2.141± 0.42	2.62± 0.49	2.63± 0.51

SD: Standard Deviation

Observing table 4.7 patients classified as IQ G registered the lowest mean weight (66.17 kg), and BMI is classified as normal (23.84). On the other hand, this group had the highest mean activity administrated (170.53 MBq; 7.23 MBq/BMI; 2.63MBq/kg) and lowest mean of interval of time (50.21 min). The opposite is observed in IQ score P where the mean weight was the highest (95.24 kg) and BMI is classified as obese (34.20). In terms of mean activity administrated this was the lowest registered (166.48 MBq; 5.03 MBq/BMI; 1.79 MBq/kg).

From now on, this study will focus on achieving a dose regime using BMI as the standard reference so all the data provide will be related to this criterion.

This criterion was chosen because patients with the same weight present different body habitus (like explained in chapter 2 subtopic 2.2.3) and like underlying before BMI followed a normal distribution in all IQ sub-groups which will make this study statically stronger.

Another point to had is looking back to the scatter plot graphs BMI versus activity/BMI is the one which stronger correlation.

Table 4.8 shows the distribution of patients according to their BMI value and IQ score.

IQ (3) - M is the one that includes more patients, 30 for observer 1 and 38 for observer 2.

Table 4.8 Number of patients per BMI in each IQ score for observer 1 and observer 2

	<18.5		**>18.5 <24.9**		**>25 <29.9**		**>30 <34.9**		**>35.0 <39.9**		**> 40 <44.9**		**>45 <49.9**		**>50 <54.9**		**TOTAL**	
OBSERVER	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**
IQ (4)	1	1	16	12	8	6	1	0	0	0	0	0	0	0	0	0	26	19
IQ (3)	0	0	4	8	19	23	4	4	2	2	1	1	0	0	0	0	30	38
IQ (2)	0	0	0	0	6	4	10	11	5	5	2	2	1	1	1	1	25	24
TOTAL	1		20		33		15		7		3		1		1		81	

Table 4.9, presents p-value when compare activity/BMI values between the different IQ scores. These values were achieved by applying t-test (before this step was taken all the groups were tested for the homoscedastic - necessary condition to be verified so t-test can be performed). Analysing the results, it can be concluded that all the comparisons are classified as significantly different, which means that in all of them the activity/BMI is different.

Table 4.9 T Test for comparison of Activity/BMI between IQ scores in observer 1 and 2

Comparisons (Activity/BMI) (p value)	**Observer**	
	1	**2**
IQ score 4 versus IQ score 3	<0.001	<0.001
IQ score 4 versus IQ score 2	<0.001	<0.001
IQ score 3 versus IQ score 2	0.007	<0.001

Figure 4.7 and 4.8 illustrate the distribution of activity/BMI for observer 1 and 2.

Different colours refer to different IQ score. It is possible to conclude that patients with lower BMI were classified with better IQ score and the inverse is observer for patients with higher BMI.

This observation can be applied for both observers.

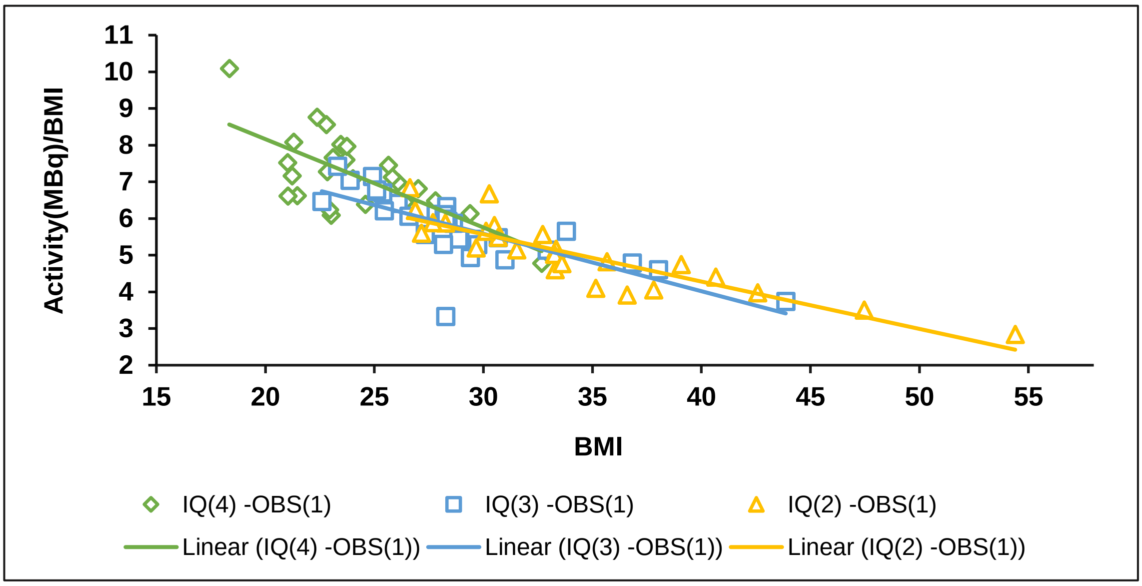


Figure 4.7 Linear correlation between BMI versus Activity/BMI in different IQ score – observer 1

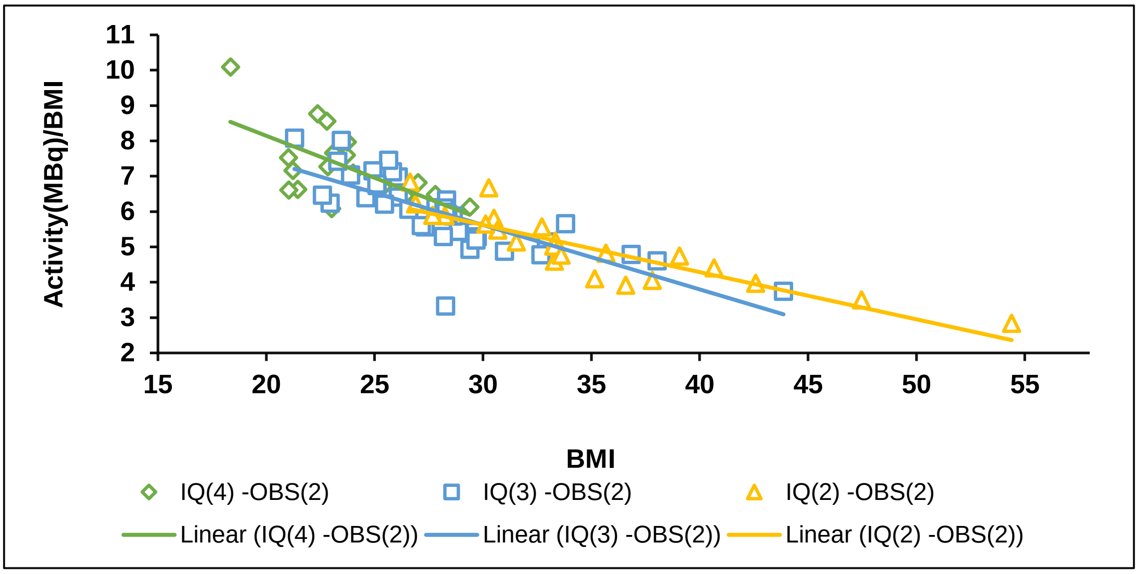


Figure 4.8 Linear correlation between BMI versus Activity/BMI in different IQ score – observer 2

Figures 4.7 and 4.8 did not consider that there were different times between injection and scanning, denominated in this study as time of interval, so to achieve this goal all the Activity/BMI were normalized.

The results are presented in table 4.10 for observer 1 and table y for observer 2.

It is possible to conclude that there a big difference between Activity/BMI when talking about normal and overweight BMI patients and when analysing the results from patients with BMI over 30.

It is important to mention that some values of Activity/BMI in IQ (2) are higher than in IQ (3) (observer (1) - BMI:]>30<34.9] IQ (3) = 4.86 but IQ (2) = 5.15 MBq/BMI or BMI:]>40 <44.9[IQ (3) =3.41 but IQ(2)=3.98).This can be explained by the size of this sample, considered small (81 patients), which can influence the results, even more when talking about BMI over 30.

Table 4.10 Observer 1 – Activity/BMI in BMI categories for different IQ scores

	Observer 1								
	<18.5	**>18.5 <24.9**	**>25 <29.9**	**>30 <34.9**	**>35 <39.9**	**>40 <44.9**	**>45 <49.9**	**>50 <54.9**	**Mean Act/BMI**
IQ (4)	9.09	6.80	6.28	4.59	0.00	0.00	0.00	0.00	6.70
IQ (3)	0.00	6.67	5.52	4.86	4.59	3.41	0.00	0.00	5.01
IQ (2)	0.00	0.00	5.71	5.15	4.03	3.98	3.10	2.87	4.14
Mean Act/BMI	9.09	6.74	5.84	4.87	4.30	3.70	3.10	2.87	

Table 4.11 Observer 2– Activity/BMI in BMI categories for different IQ scores

Observer 2									
	<18.5	>18.5 <24.9	>25 <29.9	>30 <34.9	>35 <39.9	>40 <44.9	>45 <49.9	>50 <54.9	Mean Act/BMI
IQ (4)	9.09	6.81	5.99	0.00	0.00	0.00	0.00	0.00	7.30
IQ (3)	0.00	6.70	5.63	4.78	4.59	3.41	0.00	0.00	5.03
IQ (2)	0.00	0.00	5.99	5.13	4.03	3.98	3.10	2.87	4.18
Mean Act/BMI	9.09	6.77	5.87	4.95	4.30	3.70	3.10	2,87	

Gathering all the information into table 4.12, where mean was calculated between observer 1 and observer 2, can be conclude that the highest the BMI is the lowest of Activity/BMI was administrated.

Table 4.12 Mean Activity/BMI from observer 1 and 2 for different BMI categories.

	<18.5	>18.5 <24.9	>25 <29.9	>30 <34.9	>35 <39.9	>40 <44.9	>45 <49.9	>50 <54.9
Mean Act/BMI	9.09	6.76	5.86	4.91	4.30	3.70	3.10	2.87

Repeating the process mentioned previously but this time calculating the mean between observers from IQ score, table 4.13.

Like concluded before lowest IQ score is related to lowest Activity/BMI.

Table 4.13 Mean Activity/BMI for different IQ scores.

	IQ (4)	IQ (3)	IQ (2)
Mean Activity/BMI	7	5.02	4.16

It was calculated the mean value for each BMI category referred in table 4.12. Mean values were 17 (<18.5), 22(>18.5 <24.9), 27 (>25 <29.9), 32 (>30 <34.9), 37 (>35 < 39.9), 42 (>40<44.9), 47 (>45 <49.9), 52 (>50 <54.9). New graphs were generated to assess the mean BMI versus Activity/BMI achieved in IQ (3) - M for both observers, figure 4.9 and 4.10.

It is important to mention that IQ (3) -M was chosen instead of IQ (4) - G because IQ (3) -M were considered moderate IQ which means that the clinical question can still be answered (avidity for somatostatin receptors in NET tumours) without exposing the patient to unnecessary radiation, following ALARA principle.

Before choosing an exponential function as shown in fig 4.9 and fig 4.10, other kinds of functions were tried however this was the one that gave the best correlation between the data where the r^2 in both cases it is close to 1 (observer 1 r^2= 0.9318 and observer 2 r^2= 0.938) which indicates that predictions are identical to the observed values.

Was also calculated the equation for each graph which was used to create the new BMI based injection, improving this way the IQ.

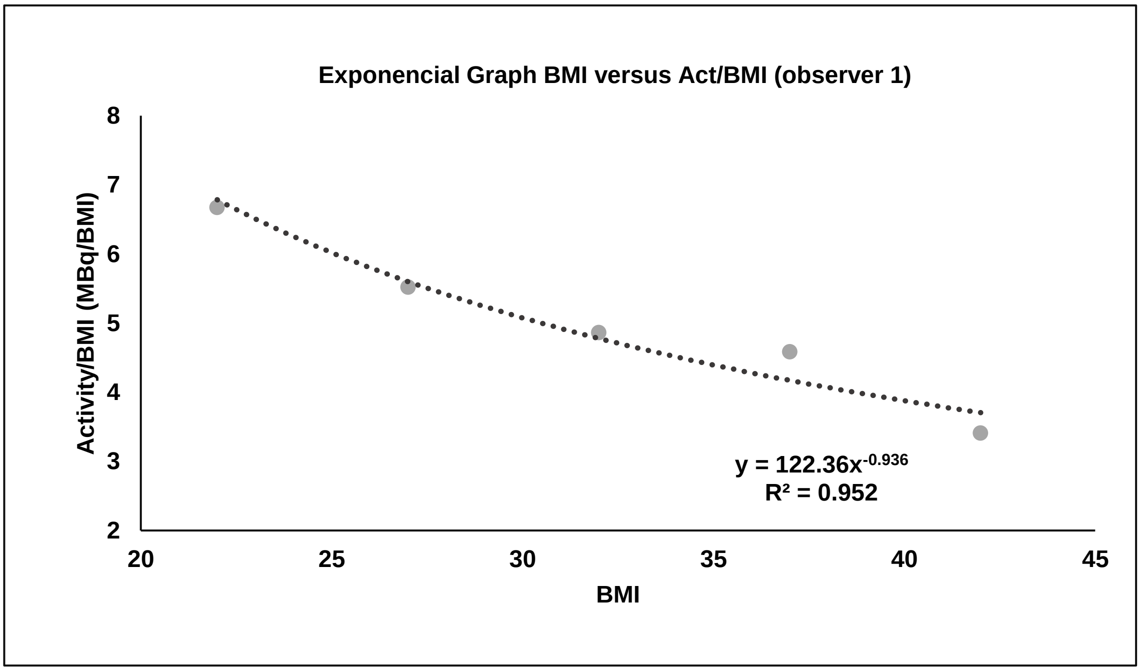


Figure 4.9 Exponential correlation between BMI and Act/BMI – observer 1

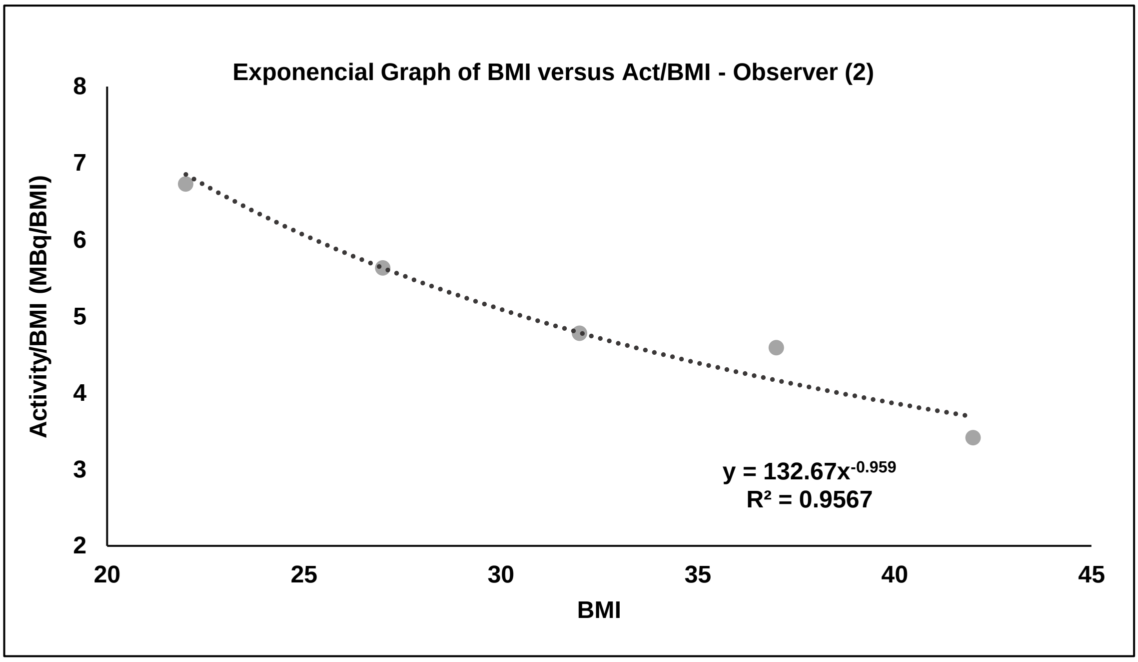


Figure 4.10 Exponential correlation between BMI and Activity/BMI – observer 2

Table 4.14 provides the minimum activity that should be injected according to the BMI to achieve IQ (3)- M.

Table 4.14 New dose regimen based on BMI for observer 1 and observer 2

Mean BMI	**Activity/BMI**		**Activity for administration**	
	Observer 1	**Observer 2**	**Observer 1**	**Observer 2**
17	8.63	8.77	147	149
22	6.78	6.85	149	150
27	5.60	5.62	151	152
32	4.77	4.78	153	153
37	4.17	4.16	154	154
42	3.70	3.68	155	155
47	3.33	3.31	157	156
52	3.03	3.00	158	157

Finally, table 4.15 demonstrate the activity to be injected when performed a mean Activity/BMI for both observers 1 and 2.

Table 4.15 New dose regimen based on BMI – mean Activity/BMI from observer 1 and 2.

Mean BMI	Activity/BMI	Activity for administration
17	8.7	148
22	6.82	150
27	5.61	152
32	4.78	153
37	4.17	154
42	3.69	155
47	3.32	156
52	3.01	158

Chapter V- Discussion

The primary indication of ^{68}Ga-DOTA-SSA PET/CT is for imaging NETs, which usually express a high density of SST receptors for localization of primary tumour and detect site of metastatic disease, follow-up patients with known disease to detect residual, recurrent or progressive disease and select patients with metastatic disease for SST receptor radionuclide therapy.[4,17]

NET are an heterogenous group of malignancies classified as rare diseases, most common found in the GI and bronchopulmonary system, like the sample used for this study also reveals. On the other hand, 9-19% of patients with NET present with metastatic disease with unknown primary tumour site, which is in line with this sample where 10% of the population does not have a primary site. Administrated activity according to patients' characteristics have been had more and more importance in the scientific community, because there is a big awareness for ALARA principles to be respected.

Most of the studies performed to achieve a regimen dose, uses weight as the patient characteristic, however in this study a new approach was follow like in *Sanchez-Jurado et al. (2014) or Xiao et al. (2021)*, where BMI was the dependent patient characteristic chosen because patients with the same weight will express different bodies habitus in accordance with their height or lean mass for example.

Cox et al. (2020) stated that they use weight as the patient parameter to achieve a dose regimen because is easy to use in practice, however BMI is easily calculated and both weight and height need to be checked prior to the scan for SUV calculations.[5]

Looking at the results obtain for mean BMI, this sample is characterized as overweight (>25 - <29.9; women= 42% and men= 39%), which is support by *Statistics on obesity, physical activity, and diet in England 2020*, where 36.2% of the population is overweight, it is also stated in this report that people aged 45-74 are most likely to be overweight or obese, which also correlate with this sample where the mean age is 63 ranging from 21-82 years.[34]

In obese and overweight patients' higher random counts, scatter activity besides attenuation and possibly pathologic hepatic heterogeneity may play a role in generating extra image noise, showing the importance of a dose regimen.[29]

Like it is known NM is really time sensitive because different radionuclides have different half-life which will influence specific organ – background target and the best interval of time to acquire the images. When talking about ^{68}Ga-DOTA-SSA PET/CT the best interval of time should be between 45-60 min, according to the UHCW protocol and EANM guidelines. This parameter was followed in this study where the mean interval of time was 54 min. Nevertheless, is important to underlying that some scans were started before or after the optimal time which could lead to decreasing of IQ.

Another point that is essential to achieve the best IQ possible is that the patient follows the preparation for this scan and no therapies been administrated according to the guidelines and UHCW protocols because this will have an impact in the SSA expression and consequently image.[3,4]

The experimental part of this project was started with the design of scatter plot graphs. This type of graphs is helpful to establish the correlation between variables for example *Cox et al. (2020)* follow this method and conclude that weight was the most correlated variable with administrated activity, however they also stated that the other patient dependent parameters were not significantly different to body mass. Some explanation for this fact is *Cox et al.* (2020) sample is smallest, only with 21 people.[5]

Other study published in April 2021 by *Xiao et al. (2021)* tried a new approach for ^{18}F-FDG PET/CT, using BMI as the patient dependent characteristic which will lead to the dose regimen. In this study BMI was determined as the best-correlated parameter with a linear fit function.[35]

IQ score was analysed by two experienced NM technologists, using a score scale commonly used in this kind of studies (Cox *et al. (2020)* and *Halpern et al (2005)*). It is important to mention that the objective in this study was concerning about the utility of the images (expressing SSA or not for further therapies and treatment), which means given the less activity possible and still be able to achieve good IQ without compromising the final diagnoses.[5]

Looking at the IQ scores no scan was categorized as ND which can be seen as positive aspect meaning that even without a dose regimen the scans still have diagnostic utility. Almost half of the sample was classified as M in observer 1 and 2 this can be correlate with the mean BMI of this sample, meaning that higher BMI would present a decrease IQ.

Observers differ their analysis in 12 patients mainly changing IQ (4) - G for IQ (3) - M , this can be explained by a more conservative approach from observer 2 and looking at some of the patients that were scored as 3 they were out of the interval of time propose by the guidelines and UHCW protocol.

This mean that some patients started their scan more than 60 min after their injection which have a big influence when talking about ^{68}Ga due to his half live of 68 min. As an example, patient number 27 was injected with 188 MBq but the scan just happened 72 min after, so the activity remained was less than 94 MBq.

When applying statical test using the IQ scores Activity/BMI was the only variable that could be classified with a normal distribution which makes this project strong when deciding to use BMI as the dependent patient parameter to achieve a dose regimen.

Most of the IQ studies performed are related to ^{18}F-FDG PET/CT because this still in the gold standard in PET/CT acquisition and the most common and available radiopharmaceutical. Hence, findings for optimized IQ with ^{18}F-FDG imaging should not be translated directly to ^{68}Ga-DOTA-SSA PET/CT.

Nevertheless,^{68}Ga-DOTA-SSA is gaining more and more space in the NM department so new studies concerning the activity to be administrated have been putting into practise and results have been published around the world in the last year. That said most of this discussion will be made with ^{18}F-FDG PET/CT studies.

The visual assessment of IQ revealed an overall substantial agreement between observers and when analysing G and M score, however there is almost a perfect agreement in P score. It is possible to observe that the characteristics for all the IQ scores do not suffer majors' changes from observer 1 and observer 2, which corroborate the Kappa Fleiss score of substantial/ almost perfect agreement between observers.

One point to underly is lowest mean BMI shows better IQ score, for example mean BMI for observer 1 and 2 as 34.0 and 34.53 (obese BMI patients) respectively in IQ (2) classified as P, on the other hand BMI for observer 1 and 2 was 24.23 and 23.84 (normal distribution BMI patients) respectively for IQ (4) classified as G.

Interesting to note that when applying statistic tests the activity administrated by BMI is significantly different between IQ scores this just show how important is to achieve a dose regimen according to patient characteristics.

Normalizing the activity administered in line with the interval of time, causes a major impact in the results because will put all the patients at the same level for example it is hard to compare patients with the same BMI and almost same amount of activity administrated when they both scanned at different time after injection. One example of that is between patient number 6 and 21 they have almost the same BMI (patient 6 =28.35 and patient 21 =28.24 with administrated activity of 167 MBq and 166MBq respectively) however time of interval is 51 min (in line with the guidelines and UHCW protocol) and 91 min respectively.

This was also done by *Groot et al. (2013)*, *and Xiao et al (2021)* with a slightly different way because both studies were working with SNR in the liver however all have the same finish line normalized the activity. SNR was used and quantitative measures/analysis were performed however when talking about ^{68}Ga-DOTA-SSA PET/CT there is not an organ defined as gold standard for SNR assessment. *Cox et al*. (2020) used the liver as organ of choice, but they had to eliminate a lot of their sample because none of the patients included in the study could have liver lesions which can be quite hard to find knowing that NET often metastasize for the entero-pancreatic system if this is not the primary site. That was one of the reasons to develop this study just with a qualitative approach.[35,43]

IQ does not mean given high doses of activity to achieve the best scan, what it means is giving the necessary to achieve a diagnostic scan following ALARA principle. Like mention previously this study had their focus in assessing how BMI influence the image and consequently how IQ can be improved especially for patient with higher BMI. That is the reason why IQ (3) -M was chosen as the spinal cord for this project where dose regimen would be calculated from.

The same principle was followed by *Wickham et al. (2017)* when identifying the SNR which will give an adequate subjective IQ was used to obtain the dose regimen. However definitely adequate was not the top of the IQ score, more than adequate classified as 5 was. This just proves the importance of follow radioprotection principles without compromising IQ, which will bring a long-term benefit because following this procedures staff and family members will have their exposed dose reduce.[44]

Graphs to achieve a dose regimen were obtained and different linear and non-linear approach were implemented, however non-linear in this case exponential graphs were the ones that best fitted the purpose of this study, the same results were achieved by *Cox et al*. (2020) were they concluded that a non-linear dose regimen is needed to achieve a more constant IQ.[5]

Groot et al. (2013), also concluded that non-linear regime seems to be a better approach that linear.[43]

Xiao et al. (2021) also reached a non-linear regime using a quadratic relation between BMI and injected ^{18}F-FDG activities, which contributes to more constant IQ not affected by BMI. [35]

It is also stated that although this regimen is less convenient than a linear relation in clinical practice it can be easily overcome by an automatic calculator or a look-up table.[35]

Like in this study the benefit of this new regime overcome the difficulties introduced. [35]

This study contradicts the ^{68}Ga-DOTA-SSA guidelines because this document recommends at least 100MBq to achieve a good IQ, however with this project even patients with underweight BMI should not be administrated with less that 140MBq.[4]

However, it is in line with the FDA recommendation for the SomaKIT TOC®, product used at UHCW to manufacture ^{68}Ga-DOTATOC where a normal patient should not receive less than 148 MBq.[34]

Chapter VI – Conclusion and Future Perspectives

^{68}Ga-DOTA-SSA have gained more and more space in the daily basis routine of a NM department, this is due to more awareness of the benefits that this scan can bring for patients with NET and more accessible prices and effective ways to produce this radiopharmaceutical without depending in external suppliers.[4,5,45]

Dose regimen based on patient dependent characteristics have received a more depth attention from the scientific community in the past years, nevertheless most of the studies performed use ^{18}F-FDG PET/CT tracer and not ^{68}Ga-DOTA-SSA, which makes this project one of the first to be executed in this area.[5,29,43,46]

With this study it is proven that BMI have a major influence in the IQ and final diagnosis, this should be considered more often because according to statistics around the world, the population in developed country which are the ones having easier access to new technology and medical developments like this radiopharmaceutical, are getting mean BMI closer to overweight and obese characteristics.[34]

Other important result from this project is time of interval can play a key role when talking about IQ and departments should be aware of it when booking and planning this kind of scans.

With this project is proven that BMI can be used to achieve a dose regimen and contradicting previous studies, dose regimen based on BMI instead of weight might bring some positive changes because more patients characteristics have been talking into account. Using BMI as the key factor is not difficult to be implement because weight and height must be measure and registered for SUV purposes.

One of the limitations of this study is the small size sample used, however this study has just been introduced at UHCW in March 2020 and during the Coronavirus pandemic a lot of studies were cancel due to government guidelines, being scan just urgent patients. Another problem faced was that the generator only lasts one year so by November it was not possible to eluate the generator with the necessary activity to achieve the minimum activity required to go ahead with the scan.

Second limitation is due to only been analyse subjective IQ, like explained before quantitative analysis are difficult in ^{68}Ga-DOTA-SSA because there is not a gold standard organ agreed by the scientific community, due to heterogeneity in the liver tissue of some patients.

Third limitations concern about the few studies performed with ^{68}Ga-DOTA-SSA, so ^{18}F-FDG PET/CT were used to support the results achieved in this project, bearing in mind that emission range for ^{18}F is different from ^{68}Ga so caution should be applied when analysing previous studies.

This project still needs to be validated including a higher number of patients from different BMI classes.

Another limitation is this study is a single-centre preliminarily study, and the BMI-based regimen needs to be further validated in a future multi-centre study.

This study just simplified the regimen as a function of the injected activity, in future study, the combination of personalized acquisition time and injected activity should be further explored, using quantitative measures such as SNR in more background regions in the body should be used, such as the spleen, blood pool (aorta) and bone marrow (vertebrae).

Other point that can be explored in future studies is how much the time of interval will influence the final image and if it is necessary to increase the time per bed when the scan is started outside of it is stipulated by the guidelines/ or department procedure.

If that is the case how much should the scanning time be increase, having in consideration that longer scanning times can lead to movement from the patient and incorrect alignment between PET and CT scans.

Reconstruction parameters to give enhancements in IQ should merited a more in-depth study, which will lead to better quantification of uptake or allow for a reduction in image acquisition time.

Trying to determine an optimal value of the noise-controlling penalisation factor β for the Q-Clear algorithm used in the GE Healthcare PET/CT scanners. This β factor can then be used to optimised SNR and consequently decrease acquisition lengths.

It is intended that, in the end, the results and conclusions of this work can elaborate a new method for calculating activity in ^{68}Ga-DOTATOC exams by PET / CT, which will be implemented in the NM department of the UHCW.

Chapter VII - References

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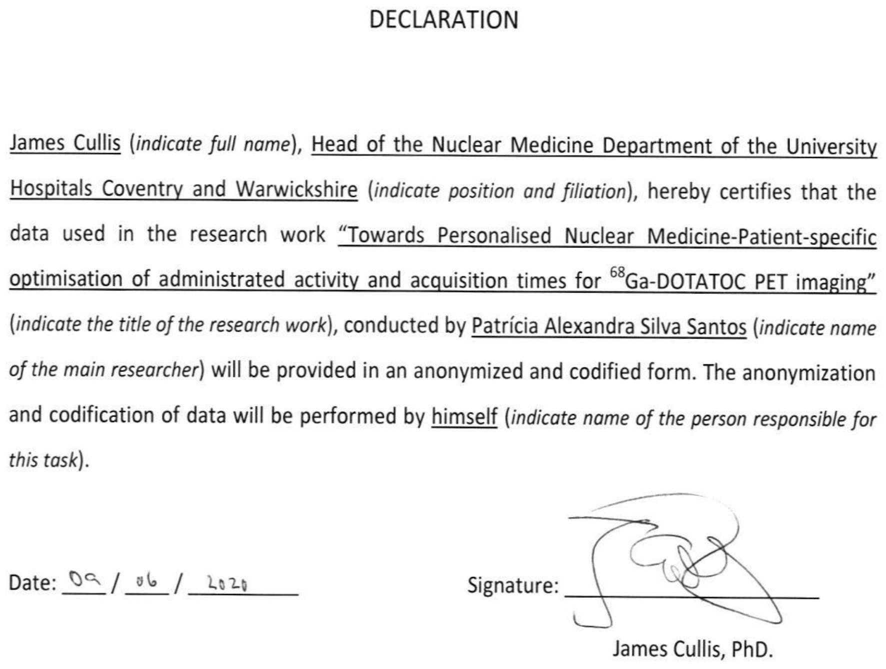
Chapter VIII- Attachments / Appendix

Appendix I



DECLARATION

James Cullis (*indicate full name*), Head of the Nuclear Medicine Department of the University Hospitals Coventry and Warwickshire (*indicate position and filiation*), hereby certifies that the data used in the research work "Towards Personalised Nuclear Medicine-Patient-specific optimisation of administrated activity and acquisition times for ^{68}Ga-DOTATOC PET imaging" (*indicate the title of the research work*), conducted by Patrícia Alexandra Silva Santos (*indicate name of the main researcher*) will be provided in an anonymized and codified form. The anonymization and codification of data will be performed by himself (*indicate name of the person responsible for this task*).

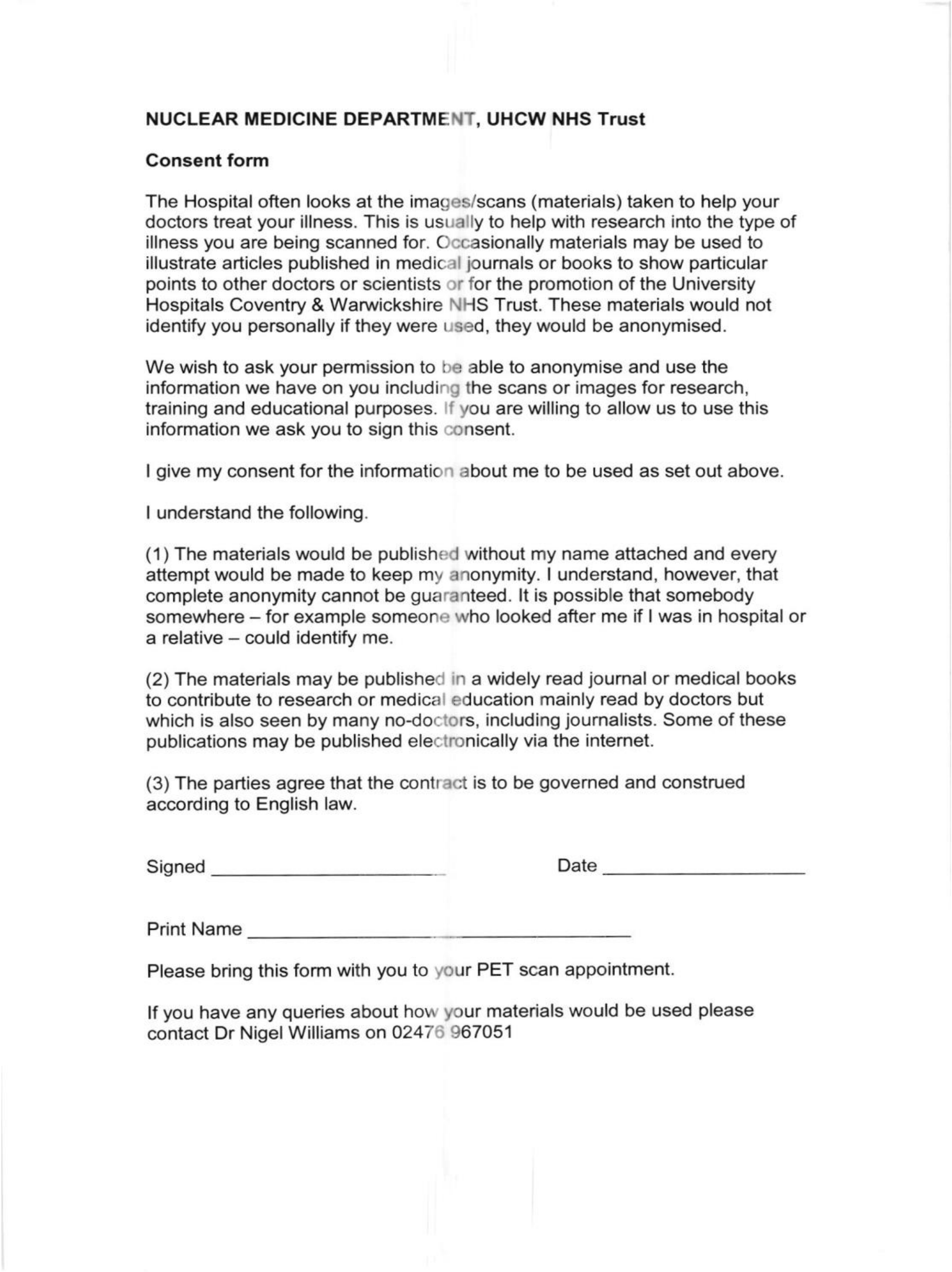
Date: 09 / 06 / 2020

Signature:

James Cullis, PhD.

Figure 8.1 Approval from UHCW to carry out the project.

Appendix II



NUCLEAR MEDICINE DEPARTMENT, UHCW NHS Trust

Consent form

The Hospital often looks at the images/scans (materials) taken to help your doctors treat your illness. This is usually to help with research into the type of illness you are being scanned for. Occasionally materials may be used to illustrate articles published in medical journals or books to show particular points to other doctors or scientists or for the promotion of the University Hospitals Coventry & Warwickshire NHS Trust. These materials would not identify you personally if they were used, they would be anonymised.

We wish to ask your permission to be able to anonymise and use the information we have on you including the scans or images for research, training and educational purposes. If you are willing to allow us to use this information we ask you to sign this consent.

I give my consent for the information about me to be used as set out above.

I understand the following.

(1) The materials would be published without my name attached and every attempt would be made to keep my anonymity. I understand, however, that complete anonymity cannot be guaranteed. It is possible that somebody somewhere – for example someone who looked after me if I was in hospital or a relative – could identify me.

(2) The materials may be published in a widely read journal or medical books to contribute to research or medical education mainly read by doctors but which is also seen by many no-doctors, including journalists. Some of these publications may be published electronically via the internet.

(3) The parties agree that the contract is to be governed and construed according to English law.

Signed ______________________ Date ____________________

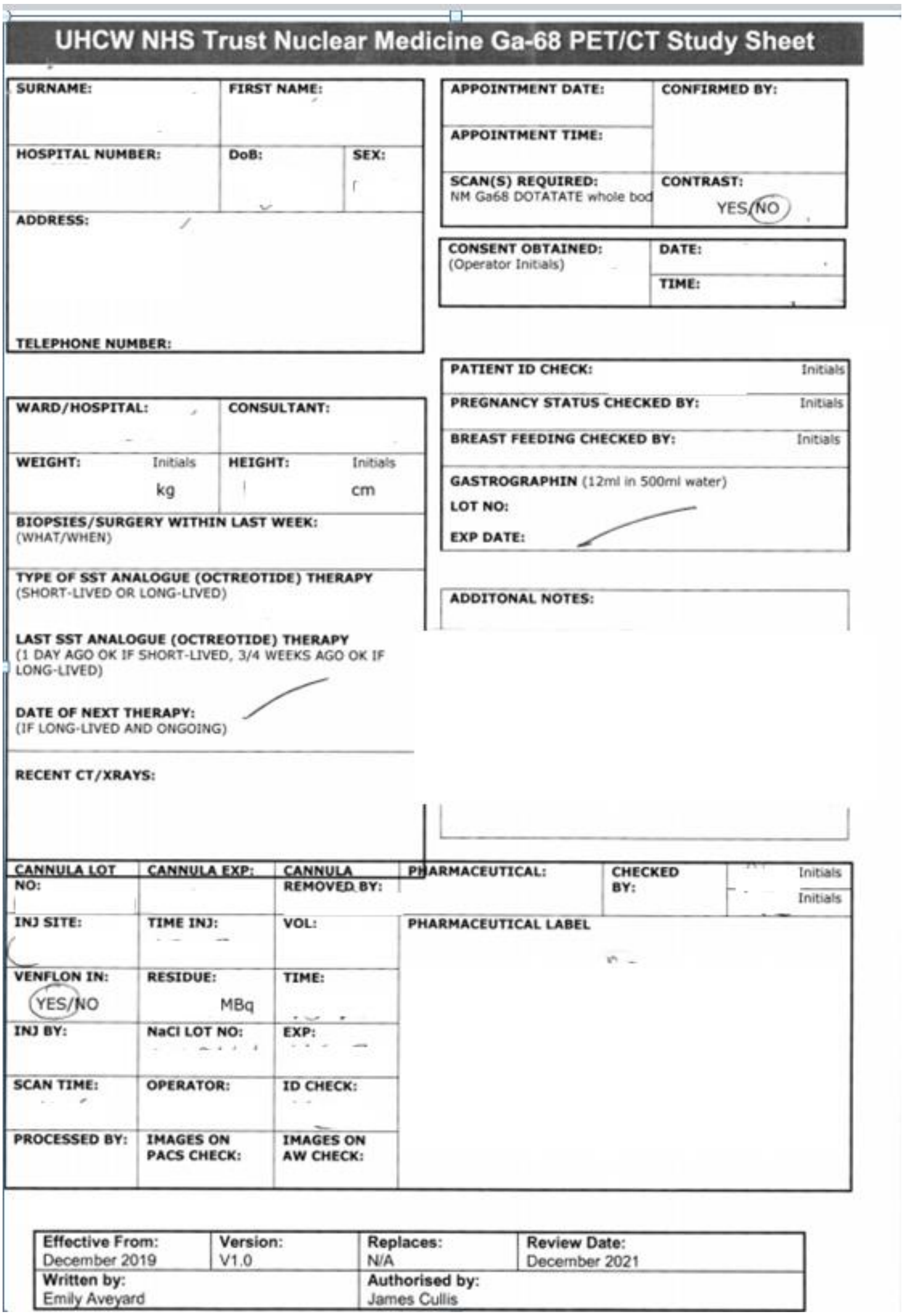
Print Name ____________________________________

Please bring this form with you to your PET scan appointment.

If you have any queries about how your materials would be used please contact Dr Nigel Williams on 02476 967051

Figure 8.2 UHCW NM consent form for PET/CT scans

Appendix III



UHCW NHS Trust Nuclear Medicine Ga-68 PET/CT Study Sheet

SURNAME:	**FIRST NAME:**	
HOSPITAL NUMBER:	**DoB:**	**SEX:**
ADDRESS:		
TELEPHONE NUMBER:		

APPOINTMENT DATE:	**CONFIRMED BY:**
APPOINTMENT TIME:	
SCAN(S) REQUIRED: NM Ga68 DOTATATE whole bod	**CONTRAST:** YES [✓ NO]

CONSENT OBTAINED: (Operator Initials)	**DATE:**
	TIME:

PATIENT ID CHECK:	Initials
PREGNANCY STATUS CHECKED BY:	Initials
BREAST FEEDING CHECKED BY:	Initials
GASTROGRAPHIN (12ml in 500ml water) **LOT NO:** **EXP DATE:**	

WARD/HOSPITAL:	**CONSULTANT:**
WEIGHT: Initials kg	**HEIGHT:** Initials cm
BIOPSIES/SURGERY WITHIN LAST WEEK: (WHAT/WHEN)	
TYPE OF SST ANALOGUE (OCTREOTIDE) THERAPY (SHORT-LIVED OR LONG-LIVED)	
LAST SST ANALOGUE (OCTREOTIDE) THERAPY (1 DAY AGO OK IF SHORT-LIVED, 3/4 WEEKS AGO OK IF LONG-LIVED)	
DATE OF NEXT THERAPY: (IF LONG-LIVED AND ONGOING)	
RECENT CT/XRAYS:	

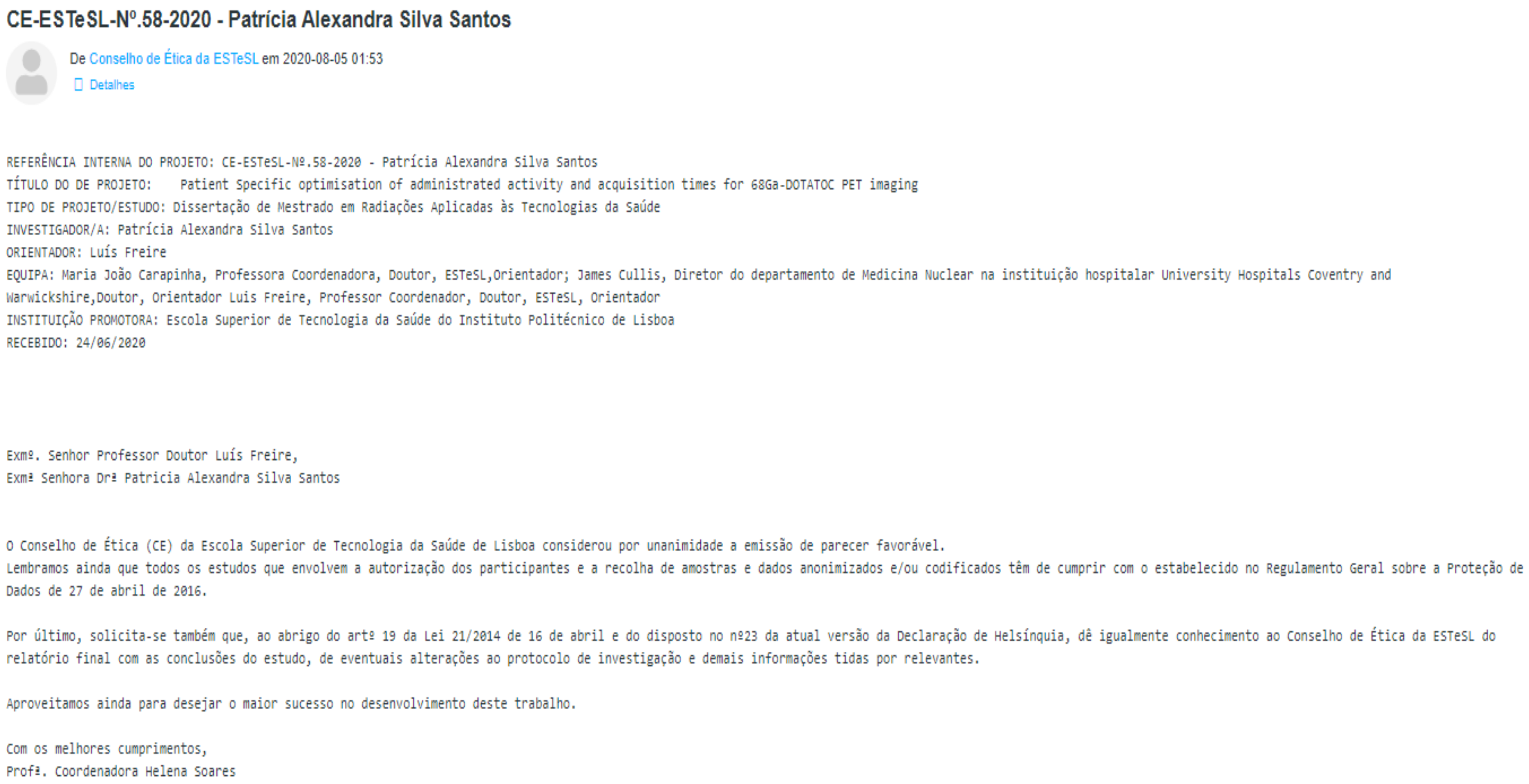
ADDITONAL NOTES:

CANNULA LOT NO:	**CANNULA EXP:**	**CANNULA REMOVED BY:**	**PHARMACEUTICAL:**	**CHECKED BY:**	Initials Initials
INJ SITE:	**TIME INJ:**	**VOL:**	**PHARMACEUTICAL LABEL**		
VENFLON IN: [✓ YES]/NO	**RESIDUE:** MBq	**TIME:**			
INJ BY:	**NaCl LOT NO:**	**EXP:**			
SCAN TIME:	**OPERATOR:**	**ID CHECK:**			
PROCESSED BY:	**IMAGES ON PACS CHECK:**	**IMAGES ON AW CHECK:**			

Effective From: December 2019	**Version:** V1.0	**Replaces:** N/A	**Review Date:** December 2021
Written by: Emily Aveyard		**Authorised by:** James Cullis	

Figure 8.3 IRMER for ^{68}Ga-DOTATOC PET -CT

Appendix IV



CE-ESTeSL-Nº.58-2020 - Patrícia Alexandra Silva Santos

De Conselho de Ética da ESTeSL em 2020-08-05 01:53

REFERÊNCIA INTERNA DO PROJETO: CE-ESTeSL-Nº.58-2020 - Patrícia Alexandra Silva Santos
TÍTULO DO DE PROJETO: Patient Specific optimisation of administrated activity and acquisition times for 68Ga-DOTATOC PET imaging
TIPO DE PROJETO/ESTUDO: Dissertação de Mestrado em Radiações Aplicadas às Tecnologias da Saúde
INVESTIGADOR/A: Patrícia Alexandra Silva Santos
ORIENTADOR: Luís Freire
EQUIPA: Maria João Carapinha, Professora Coordenadora, Doutor, ESTeSL,Orientador; James Cullis, Diretor do departamento de Medicina Nuclear na instituição hospitalar University Hospitals Coventry and Warwickshire,Doutor, Orientador Luis Freire, Professor Coordenador, Doutor, ESTeSL, Orientador
INSTITUIÇÃO PROMOTORA: Escola Superior de Tecnologia da Saúde do Instituto Politécnico de Lisboa
RECEBIDO: 24/06/2020

Exmº. Senhor Professor Doutor Luís Freire,
Exmª Senhora Drª Patricia Alexandra Silva Santos

O Conselho de Ética (CE) da Escola Superior de Tecnologia da Saúde de Lisboa considerou por unanimidade a emissão de parecer favorável.
Lembramos ainda que todos os estudos que envolvem a autorização dos participantes e a recolha de amostras e dados anonimizados e/ou codificados têm de cumprir com o estabelecido no Regulamento Geral sobre a Proteção de Dados de 27 de abril de 2016.

Por último, solicita-se também que, ao abrigo do artº 19 da Lei 21/2014 de 16 de abril e do disposto no nº23 da atual versão da Declaração de Helsínquia, dê igualmente conhecimento ao Conselho de Ética da ESTeSL do relatório final com as conclusões do estudo, de eventuais alterações ao protocolo de investigação e demais informações tidas por relevantes.

Aproveitamos ainda para desejar o maior sucesso no desenvolvimento deste trabalho.

Com os melhores cumprimentos,
Profª. Coordenadora Helena Soares

Figure 8.4 ESTeSL Ethical Committee – approval