Towards clinical implementation of quantitative PET and SPECT imaging

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CHAPTER 1

General introduction and outline

Since its introduction in the late 1940s, nuclear medicine has become essential in healthcare for diagnosis, staging, and treatment by providing unique insights into in vivo physiological and metabolic functions. Nuclear imaging makes use of radiotracers, small amounts of chemical compounds labelled with radioactive isotopes, to image the distribution of the radiotracer within the body [1]. Attributed to a variety of radiotracers that have been developed, multiple tissue functions can be visualized including perfusion, metabolism, receptor systems and hypoxia [2], offering insights across various medical disciplines. Single Photon Emission Computed Tomography (SPECT) is the most widely adopted camera using gamma-emitting radiotracers to generate three-dimensional (3D) images of the body. Another frequently used nuclear imaging technique is Positron Emission Tomography (PET) which detects pairs of annihilated gamma photons emitted by positron-emitting isotopes to compose a 3D image. Integrating SPECT or PET with Computed Tomography (CT) provides anatomical information and enables attenuation correction by compensating for photon absorption in different tissues. [2, 3]

Qualitative image evaluation, which relies on the visual interpretation of radiotracer uptake and tissue density on CT, has been the primary approach in nuclear imaging since its introduction in healthcare. This method is essential for diagnosing diseases and assessing their presence and progression. The limitation of visual interpretation is that it might lead to observer variability, causing inconsistent and unreliable imaging data interpretations. Especially when we want to monitor the course of a disease or determine the response to therapy, we need to be able to measure whether there is an increase or decrease in tracer uptake. In such cases, in addition to visual inspection, accurate quantification tools are highly beneficial, and almost unaffected by inter-observer variability. Quantifying radioactivity concentration within a tissue volume supports personalized treatment through dosimetry calculations, optimizing therapeutic efficacy, while also enabling early disease detection by identifying subtle metabolic changes before structural abnormalities become apparent on conventional imaging [4]. Recent developments in nuclear medicine have enabled (semi-)quantitative analysis as a complementary assessment to visual interpretation, enabling objective measurements of concentrations of radiotracers in tissues, metabolic rates, and functional activity of organs.

QUANTITATIVE PET/CT

PET is widely known as a quantitative imaging tool due to its ability to calibrate voxel values in reconstructed images to absolute units of radioactivity concentration with high accuracy and precision [5]. This facilitates accurate interpretation of PET images by representing underlying physiology in absolute units and enables tracer kinetic modelling

for quantifying physiological parameters. Various factors influence the accuracy of PET imaging. Count-rate losses, detector efficiency variations, scattered coincidences, and signal dilution (partial volume effect), amongst others, significantly affect PET accuracy, necessitating precise corrections to preserve image quality [2]. Advances in radiotracer development, image reconstruction algorithms, and correction methods continue to enhance the capabilities of PET/CT. The implementation of quantitative PET/CT is slowly expanding within clinical practice.

Standardized Uptake Value (SUV) is commonly used for assessing radiotracer uptake in tumors and other tissues [6]. The SUV, measured in [g/mL], represents the ratio of the local activity concentration to the decay-corrected quantity of injected radiotracer predominantly per unit of body weight. This metric reflects the concentration of the radiotracer in a particular area relative to its uniform distribution across the body. SUV is useful for comparing measurements within an individual against standard values from a reference population. Additionally, it enables the longitudinal tracking of subtle changes in the body, whether due to disease progression, response to therapy, treatment related effects on (normal) tissues or physiological day-to-day variations in the human body.

A single static image can be captured at a specific moment after radiotracer injection, or the radioactivity can be continuously monitored over time. When the right radiotracer is chosen and suitable imaging conditions are applied, the activity values measured in a region of interest (ROI) in the image should primarily reflect the physiological characteristic of interest, such as blood flow, metabolism or receptor concentration. A kinetic model seeks to describe the relationship between these measurements and the parameters of interest. Essentially, an accurate tracer kinetic model can account for a proximity of the biological factors contributing to the tissue radioactivity signal. Kinetic tracer modelling, including dynamic PET analysis, are employed to measure absolute parameters such as blood flow, volume of distribution, metabolic rate and binding potential. [5]

Advancements in PET/CT technology have improved image quality and sensitivity, enhancing diagnostic accuracy and potentially improving patient outcomes [7]. The integration of precision deep learning-based image enhancement further sharpens features and accelerates convergence [8]. Increased sensitivity enables possibilities to reduce both scan duration and/or the administered activity of radiopharmaceuticals. Shorter scan durations may enhance patient comfort, increase patient throughput and decrease motion effects. [9]. However, limited literature exists on cutting-edge PET/CT systems, making a thorough evaluation of their scan-time and administered activity reduction capabilities essential before widespread implementation.

QUANTITATIVE SPECT/CT

Historically, gamma cameras assessed relative uptake of radiopharmaceuticals, while PET imaging provided absolute quantification with units like kBq/mL that can be used for detailed 3D disease assessment. Although, in a clinical setting, SPECT/CT was once seen as less advanced than PET/CT, recent advancements in iterative image reconstruction have improved its capabilities. These advancements allow (semi-)quantification of SPECT/CT by incorporating compensation for collimator–detector response, photon attenuation, and scatter, as well as resolution recovery into the reconstruction process, greatly enhancing its quantitative accuracy. [10] Consequently, SPECT/CT enables the measurement of (semi-)quantitative imaging features based on SUV, leading to more accurate measurements for various clinical applications.

However, quantitative SPECT presents more challenges compared to PET due to the increased number of variables involved, including radionuclides with differing photon energies, various collimators, the possibility of using multiple energy windows, and the potential for performance drifts given the greater number of moving parts in a SPECT system [11]. Despite these complexities, SPECT is evolving from a primarily qualitative modality to one that also incorporates (semi-)quantification for clinical evaluation.

AIM

Quantitative PET and SPECT have significantly advanced over the past decades and are integrated into clinical guidelines, particularly for oncology, neurology, cardiology, inflammation and infection. However, there is substantial potential for broader use of quantitative PET and SPECT across other indications and fields, suggesting that existing capabilities remain underutilized. A key barrier is the lack of robust evidence, underscoring the need for further research to validate their expanded applications, including in drug development. This would support the development of tailored treatment plans, ultimately improving outcomes across a wider range of diseases.

The general aim of this thesis is to deepen the understanding of quantitative PET and SPECT in clinical settings, explore their potential beyond current applications, and establish a foundation for their broader implementation in clinical practice.

OUTLINE OF THESIS

This thesis consists of two parts. **Part 1** explores two novel applications of quantitative PET/CT and focusses on a novel PET/CT scanner with precision deep learning for improved feature sharpness comparable to time-of-flight reconstruction.

Assessing renal perfusion in-vivo is challenging and quantitative information regarding renal hemodynamics is hardly incorporated in medical decision-making while abnormal renal hemodynamics might play a crucial role in the onset and progression of renal disease. Combining physiological stimuli with [^{82}Rb]Cl PET/CT offers opportunities to test the kidney perfusion under various conditions. **Chapter 2** investigates the application of a one-tissue compartment model for measuring renal hemodynamics using dynamic [^{82}Rb]Cl PET/CT imaging, and whether dynamic PET/CT is sensitive to detect differences in renal hemodynamics in stress compared to rest.

Since the end of 2019, the coronavirus disease 2019 (COVID-19) virus has infected millions of people, of whom a significant group suffers from sequelae from COVID-19, termed long COVID. **Chapter 3** outlines the potential added value of non-metabolizable glucose analogue 2-[18F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG)-PET/CT for this group of long COVID patients.

The enhanced sensitivity allows shorter scan durations, improving patient comfort, throughput, and reducing motion effects, or lowering the administered radiopharmaceutical activity to save costs and minimize radiation risks for staff and patients. Furthermore, a lower dose and/or reduced costs could potentially open up new applications for (quantitative) PET. **Chapter 4** assesses the lower [^{18}F]FDG limit in administered activity and/or scan time reduction capabilities of a digital bismuth germanium oxide 32-cm axial field-of-view PET system while being compliant with current and updated EANM Research Ltd Fluorine-18 accreditation specifications ($EARL_1$ and $EARL_2$, respectively).

Part 2 presents two potential clinical applications of quantitative SPECT/CT. **Chapter 5** investigates the quantitative accuracy and precision of a novel iterative reconstruction technique for the potential application of response monitoring using [^{99m}Tc]Tc-tetrofosmin SPECT/CT in patients with coronary artery disease. **Chapter 6** evaluates the semi-quantitative SPECT parameters of prone SPECT using [^{99m}Tc]Tc-sestamibi and compares them with Molecular Breast Imaging (MBI)-derived semi-quantitative parameters for the potential use of response prediction in women with locally advanced breast cancer.

Chapter 7 provides a summary, general discussion and future perspectives in English and **Chapter 8** a summary in Dutch.

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