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New PET technologies
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Chapter 1

General introduction

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PET principles

Positron Emission Tomography (PET) is the most specific and sensitive imaging modality for visualizing and measuring human physiology *in vivo* (1). This nuclear medicine imaging modality is based on the intravenous injection of radiotracers labeled with a positron-emitting radionuclide (2). When a positron-emitting radionuclide decays in the body, interaction of the positron with an electron results in an annihilation event emitting two 511 keV annihilation photons in nearly 180-degree opposite directions. The simultaneous emission of these photons sent towards detector rings surrounding the patient form the basis of the detection and localization of positron emitters via a mechanism called coincidence detection (4,5). This process allows localization of the annihilation event to somewhere on the line of response (LOR) connecting the detectors on either side of the detector ring. Typically, approximately 10^7 to 10^8 coincidence events are collected by the detectors which are used to reconstruct a PET image reflecting the distribution of the radionuclide in the body (2).

^{18}F-FDG PET

The most commonly used PET tracer is the glucose analogue ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) and is based on the principle that ^{18}F-FDG accumulation in tissue is proportional to the amount of glucose utilization (4,5). The research described in this thesis primarily focused on PET using ^{18}F-FDG which contains ^{18}F, a cyclotron-produced positron-emitting radioisotope of fluorine. ^{18}F-FDG has a short half-life of 109.7 min and the low positron energy (640 keV) results in short tissue range which is translated into relatively low radiation dose and high resolution (6). Various molecular tracers can be labeled with ^{18}F and imaged within a few hours, typically <3 h, after injection. Many cancers demonstrate increased consumption of glucose, which is, in part, related to over-expression of the GLUT-1 glucose transporters and increased hexokinase activity. Once inside the cell, ^{18}F-FDG is phosphorylated by hexokinase into ^{18}F-FDG-6-phosphate, which, unlike glucose, because of chemical differences cannot be further metabolized ensuring metabolic trapping (6). For clinical use, static mages are most frequently acquired at approximately 60 min post ^{18}F-FDG radiotracer injection. In oncology, ^{18}F-FDG PET has become part of the daily clinical routine including initial diagnosis, staging, prognosis, radiation therapy planning, and monitoring response to treatment (7-10).

[89]Zr immunoPET

Zirconium-89 ([89]Zr) is also a cyclotron produced positron-emitting radioisotope. [89]Zr decays with a half-life of 78.4 hours, first via positron emission and electron capture to the meta-stable yttrium-89m ([89m]Y), with a half-life of 15.7 s, which

subsequently decays via gamma ray emission (909 keV) to the stable ^{89}Y (11,12). ^{89}Zr labeled monoclonal antibodies (mAb) are another type of tracers used in the research described in this thesis. Numerous advantages of ^{89}Zr such as the long half-life of 78.4 hours, matching the pharmacokinetic behavior of antibodies, and good *in vivo* stability, make it a suitable candidate for labeling of mAb (13). ^{89}Zr immunoPET provides whole body information on (tumor) target expression (14). The low positron abundance of ^{89}Zr (23%, as opposed to ^{18}F with an abundance of 96%) (13) causes PET images acquired on conventional PET/CT systems to have a low signal to noise ratio (SNR). In addition, the long physical half-life limits the amount of radiotracer activity that can be administered to patients in order to keep radiation exposure within acceptable limits (15). Hence, to obtain sufficient count statistics on conventional PET/CT systems for adequate image quality, long scan durations are required, especially at later scan time-points.

ToF application

Use of time-of-flight (ToF) information can increase the accuracy of localizing the annihilation event along the LOR. The emission distance (d) along this LOR can be calculated using Eq. 1:

$$d = c * (t_1 - t_2)/2$$ *Eq. 1*

Here, c represents the speed of light and t_1 and t_2 are the times the coincidence photons are captured by the opposing detectors. In non-ToF PET, the PET system is not capable of measuring the difference in arrival time (t_2-t_1) of the photons precisely enough to determine the location of the annihilation event along the LOR (16,17). Consequently, the probability of the annihilation event along the full length of the LOR is assumed to be uniform over the length of the LOR. Therefore, information from different events is forward- and backward-projected during (iterative) image reconstruction over the entire length of the LOR resulting in slower reconstruction convergence and increased noise levels (or worse SNR) as compared when ToF information would be available during reconstruction, as detailed later. Around the year 2005, improved system characteristics and electronics optimized for ToF imaging, e.g., use of lutetium oxyorthosilicate (LSO) or lutetium-yttrium oxyorthosilicate (LYSO) scintillation crystals with high count rate capabilities and photomultiplier tubes (PMTs) with good timing performance, allowed the first commercial introduction of ToF-PET. Application of ToF in PET image reconstruction allows localization of the annihilation event within a small region of the object along the LOR, i.e., several cm. The system coincidence timing resolution (Δt) determines the uncertainty in corresponding spatial localization (Δx) according to Eq. 2:

$$\Delta x = c * \Delta t/2 \qquad\qquad \textit{Eq. 2}$$

Here, c represents the speed of light.

During reconstruction with ToF, due to a smaller spatial uncertainty, noise from different annihilation events is now forward- and backward-projected over a reduced number of image voxels leading to improved SNR, as well as a faster image reconstruction convergence (18). A reduction of noise can be equated with an increase in sensitivity, the effective sensitivity gain, which can be calculated using Eq. 3, the modified Budinger's equation (19):

$$ToFgain = \frac{1}{1.47}\frac{D}{c/2\Delta t} \qquad\qquad \textit{Eq. 3}$$

Here, D is the transverse diameter of the average human abdomen in cm. Eq. 3 can be simplified to Eq. 4:

$$ToFgain = constant * D/\Delta t \qquad\qquad \textit{Eq. 4}$$

The *constant* can then be calculated using Eq. 5:

$$constant = \frac{2/(1.47 * c)}{1\ ps} = 45.38 \qquad\qquad \textit{Eq. 5}$$

When taking 30 cm as the average human abdominal transverse diameter, *ToFgain* can be calculated using Eq. 6:

$$ToFgain = 45.38 * 30/\Delta t \qquad\qquad \textit{Eq. 6}$$

The effective sensitivity can subsequently be calculated according to Eq.7:

$$Sens_{eff} = Sens * ToFgain \qquad\qquad \textit{Eq. 7}$$

These metrics provide an indication that ToF gain increases with improved coincidence timing resolution, but also with increasing patient size (20). As conventional PET image quality deteriorates considerably with increasing patient size because of increased attenuation causing both loss of true counts and increase of scattered counts, improved image quality with ToF application due to improved SNR and effective sensitivity gain is a powerful tool right where it is needed most (17,20).

Digital PET

Over the last decades, the main development in PET detector design has been the adoption of solid-state technology (18). Conventional PMTs have been replaced by solid-state read-out devices in recently introduced commercially available PET/CT systems. This detector technology has the advantage of being compact, but its insensitivity to a magnetic field makes it well-suited for PET coupled with Magnetic Resonance Imaging as well. The first clinical PET/MRI systems manufactured by Siemens (Siemens Healthineers, Knoxville, TN, USA) were equipped with avalanche photodiodes (APDs). More recently, further development of APDs resulted in the introduction of silicon-photomultipliers (SiPMs) which are implemented also in the latest clinical PET/CT systems.

An APD is formed by a silicon p-n junction creating a depletion region free of mobile charge carriers. When a 511-keV photon is absorbed in a light-sensitive layer, silicon, an electron-hole pair is created (photo-electric effect). When applying a reverse bias to the photodiode, an electric field will be created across the depletion region causing these charge carriers to be accelerated towards the anode (holes), or cathode (electrons). This way, an absorbed photon will result in a net flow of current in a reverse biased APD.

The applied electric field causes acceleration of electrons which in turn produce a secondary ionization, or avalanche, resulting in amplification of the electric signal. However, this gain is not as high as with conventional PMTs. The slow rise time of the signal makes APDs unsuitable for implementation of ToF PET. In ToF PET, as described above, the difference in the arrival times of the two photons on both detectors is measured with high precision, which helps localize the point of annihilation (with a certain probability) along the line of response (21). However, when the applied reverse-bias voltage is increased sufficiently (approaching the breakdown voltage) a created charge carrier will be accelerated to such an extent that it carries sufficient kinetic energy to create secondary charge pairs; this process is referred to as impact ionization. Accordingly, a single absorbed photon can trigger a self-perpetuating ionization cascade spreading through the silicon volume subjected to the electric field. Breakdown of the silicon occurs making it conductive, effectively amplifying the original electron-hole pair into a macroscopic current flow. This is called Geiger discharge; the APD operates in Geiger mode. Then, a single incoming light photon produces a large signal and the device is referred to as a single-photon avalanche diode (SPAD) of very compact size (10-100 μm) (22,23). Once a current is running it should be stopped or 'quenched'. Passive quenching is achieved through using a series of resistors which limit the current drawn by the diode during breakdown. This

lowers the reverse voltage seen by the diode to a value below its breakdown voltage. The diode is then available to detect subsequent photons. Through this mechanism, a single SPAD functions as a photon-triggered switch, in either 'on' or 'off' state, resulting in a binary output. Proportional information regarding the photon flux is not available. This lack of proportionality is overcome in the SiPM. An SiPM is comprised of an array of (between 100 and 10,000) SPADs which are read-out in parallel producing an electric signal proportional to the number of detected 511-keV photons in a small detector area (cell). The gain and detection efficiency are comparable to conventional PMTs while using a smaller operating voltage and running at a higher speed. An array of SiPMs can be used instead of the conventional array of PMTs (18).

Currently, there are three different commercially available 'digital' PET/CTs available which are equipped with SiPM-based PET detectors: the Siemens Biograph Vision PET/CT (Siemens Healthineers), the Philips Vereos PET/CT (Philips Healthcare), the GE Discovery MI PET/CT (General Electric Healthcare).
Two different types of SiPM-based PET detectors are currently implemented in the abovementioned three systems. On the one hand there are so called analog SiPM-based detectors and on the other hand digital SiPM-based detectors or Digital Photon Counters (DPC). The analog design incorporates the connection of multiple SiPM arrays together to sum the signals from each SiPM for a summed output (as implemented in the Biograph Vision and the GE Discovery MI PET/CT). The digital approach considers each SiPM separately to achieve a single readout for each SiPM (as used in the Philips Vereos PET/CT) (22).

Benefits of digital PET

The first generation ToF PET/CT systems achieved a system sensitivity of 5-10 kcps/MBq with a timing resolution of 450-600 picoseconds (ps). The sensitivity is largely dependent on the length of the axial field-of-view (FOV), ranging from 16-21 cm. The system spatial resolution of 4 to 5 mm was mostly determined by the use of PMT in combination with somewhat larger detector or crystal element, but also linked to the available sensitivity and acceptable clinical scan durations. For improved spatial resolution, a substantial increase in sensitivity (i.e., count statistics) would have been required to maintain similar noise levels (24).

With the introduction of digital PET/CT systems, ToF improved to a range of 210-400 ps because of implementation of SiPMs with superior coincidence timing compared with PMTs, and an increased sensitivity of up to 20 kcps/MBq due to a longer axial FOV was achieved (18,24). Because of the compact size of SiPM-based detector

elements, crystals of less than 4x4 mm in cross section could be used allowing improved spatial resolution. The improved physical performance characteristics translated to a more sensitive and efficient use of digital PET systems in clinics.

The increased spatial resolution, providing higher measured contrast, combined with a higher sensitivity and improved ToF result in better noise properties. Consequently, improved imaging capabilities of digital PET systems can be used to obtain comparable image quality with a factor 3 shorter scan time (or reduced radiotracer activity) (24,25). Alternatively, improved imaging performance can be used to obtain images with better image quality which may lead to improved clinical diagnostic capabilities, especially for detecting small (tumor) lesions.

LAFOV PET

The latest development in PET/CT system design has been the introduction of the 'total body' PET system, i.e., long axial FOV (LAFOV) PET system, which holds promising opportunities for future research and patient care. Also equipped with SiPM-based detectors, these systems surround the patient with many more detectors in the axial FOV direction which comes with two major improvements (26):

1. Longer axial extent of the FOV resulting in higher detection efficiency as more photon pairs are captured.
2. One bed position covers a much larger proportion of the patient, thus the same time frame can cover more anatomy.

Three LAFOV systems have so far been introduced. These are the PennPET Explorer (University of Pennsylvania) (27,28) with a 64-cm-long axial FOV, the uEXPLORER (United Imaging Healthcare) (29) which has a 194-cm-long axial FOV, and the Siemens Biograph Vision Quadra PET/CT (Siemens Healthineers) (30) with a 106-cm-long axial FOV.

The substantially increased sensitivity of LAFOV PET systems will allow an even larger reduction in scan time and/or amount of radiotracer administration with respect to digital PET systems, but these systems come with many other opportunities yet to be explored (31,32).

Quantification
SUV

Acquired PET images can be interpreted visually, e.g., for staging, or semi-quantitatively, e.g. to determine treatment-response, which requires standardized and harmonized imaging procedures, especially in a multicenter setting (33). The semi-quantitative standardized uptake value (SUV) of ^{18}F-FDG, derived from static images obtained at 60 minutes postinjection (p.i.), is most commonly used as a

surrogate of metabolic activity for tumor uptake quantification (5,34). To quantify treatment response, patients are classified into response categories based on the relative SUV measurement change; response categories include complete response, partial response, stable disease, and progressive disease. Subsequently, clinical treatment decisions and a prediction of clinical outcome can be guided by these response classifications (35).

When procedure guidelines for standardized tumor imaging such as the European Association of Nuclear Medicine (EANM) procedure guidelines with standardized protocols regarding patient preparation, PET image acquisition, reconstruction settings, and analysis methods are followed, repeatable and reproducible PET acquisition is facilitated (4,34). Subsequently, PET images can be converted reliably to SUV (for most clinical cases) normalizing the radioactive activity concentration as visualized in the image by body weight and amount of injected tracer dose according to Eq. 8:

$$SUV_{BW} = \frac{c_t [kBq/mL]}{Dose[MBq]/weight[kg]} \qquad Eq.\ 8$$

Here, SUV_{BW} represents the calculated SUV corrected for bodyweight, c_t is the measured concentration of the tracer in tissue, and the denominator contains the injected dose in MBq and the subject's weight in kg. Herein, bodyweight can sometimes be replaced by body surface area, lean body mass (SUL), or BMI. Using SUV as a metric of relative tissue uptake normalized to the average radioactivity concentration in the body facilitates longitudinal intrapatient- as well as interpatient comparisons (36).

SUV and other PET image biomarkers can be obtained after segmenting a volume of interest (VOI), in tumor lesions or background tissue. Three most commonly derived SUV are SUV_{max}, SUV_{peak}, and SUV_{mean}. SUV_{max} represents the highest uptake of a single voxel in the VOI. SUV_{peak} represents the highest average uptake in a 1 mL area in the defined VOI and SUV_{mean} is simply the VOI's average SUV (35). Because SUV_{max} is a single voxel value, it is adversely affected by noise (37,38) leading to quantitative uncertainty. As SUV_{peak} represents the average SUV in a small fixed-size VOI centered on the highest-uptake part of the total segmented (tumor lesion) VOI, it has been suggested as a more robust alternative (33). However, both SUV_{max} and SUV_{peak} are less observer dependent than SUV_{mean}. SUV_{mean} requires reproducible segmentations because it depends on the total VOI, i.e., it depends on the observers' manual or semi-automated VOI definition.

Standard PET-based segmentation methods to define tumor VOIs and derive PET

image biomarkers, such as SUV, include manual segmentation or semi-automated segmentation. Where manual segmentations can be labor- and time-intensive, and prone to both intra- and interobserver variability, a single widely available and accepted semi-automated method is currently lacking. The EANM Research Limited (EARL) guidelines (34) recommend segmentations based on fixed SUV VOI thresholds of 2.5 or 4.0 g/mL, 41% or 50% of the lesion's SUV_{max}, and 50% of the lesion's SUV_{peak} adjusted for background uptake (39-41).

Patlak

Simplicity and use of an easy static imaging procedure are two of the most important benefits of using SUV, however, measurements are also vulnerable to unwanted variability (37,42). Following standardization methods, such as the EANM procedure guidelines for tumor imaging, can mitigate SUV variability to a great extent (34,43,44). However, these standardization methods are not able to account for changes in plasma kinetics, due to e.g., treatment, or distinguish between specific and nonspecific uptake possibly causing a dissociation between inaccurate SUV measurements and actual tumor metabolic activity (45-48). In contrast, dynamic whole body ^{18}F-FDG PET imaging is able to include this information as it allows spatiotemporal activity concentration measurement, providing voxel-wise metabolic information, i.e., the ^{18}F-FDG influx rate constant (K_i), after applying full kinetic- or Patlak analyses (49-51). In order to generate whole body parametric PET images, the slow kinetics of ^{18}F-FDG require scanning for at least a duration of 45 to 60 min (52).

In current clinical practice, there are two ways to acquire whole body dynamic PET images noninvasively:

1. On a Biograph Vision PET/CT system where a combined acquisition of first 6 min of dynamic imaging over the heart, to obtain the arterial image derived input function (IDIF), followed by multiple whole body sweeps up to 60 min p.i.
2. On an LAFOV system where the long axial coverage captures the heart, to derive the IDIF, and all other organs of interest, including possible tumor lesions, within a single bed position.

For the analysis, a VOI is typically placed in the ascending aorta (53) to obtain the IDIF. Then, to determine K_i and the total blood distribution volume V, the measured tissue time-activity curve (TAC) from the PET image and the IDIF serve as input for a voxel-wise Patlak analysis according to Eq. 9 (54):

$$\frac{C(t_n)}{C_P(t_n)} = K_i \frac{\int_0^{t_n} C_P(\tau)d\tau}{C_P(t_n)} + V, t_n > t^*, n = 1 \dots N \qquad Eq.\ 9$$

Where $C(t)$ is the measured TAC at each voxel, $C_P(t)$ the IDIF, and t_n with $n=1\dots N$

represents the mid-time points for the N dynamic PET frames. t^* is the time after which relative kinetic equilibrium between blood and the reversible compartment is assumed, i.e., when the Patlak plot becomes linear.

With regard to clinical advantages of whole body dynamic Patlak imaging over conventional static scans, parametric images can provide complementary information to standard SUV images, or rather filter information by deleting intravascular contributions to the PET signal, enabling easier detection and classification of small ^{18}F-FDG avid lesions, particularly in high background uptake regions, such as the liver (55,56). However, new generation PET systems, including LAFOV systems, allow standard whole body static scans of less than 2 min (28,57,58). Including patient positioning and acquisition of a CT, this could lead to a total examination time of approximately 10 to 15 min. Taking into account patient comfort and desired patient throughput at different PET centers, dynamic whole body Patlak imaging may not be suitable for all patient studies; for diagnostics and staging, a simple static scan would do. However, for select patient groups, additional information to more accurately monitor treatment response may be required, especially when comparing to a baseline scan. In those cases ^{18}F-FDG blood clearance changes may affect SUV-based quantification (45,48,56,59,60).

Thesis aim

The aim of this thesis is to characterize the performance two innovative newly introduced PET/CT systems and to highlight the benefits and opportunities of these new PET/CT system technologies for direct clinical application and future scientific research.

Thesis outline

This thesis starts with an extended introduction on digital PET. **Chapter 2** describes the technical principles regarding digital PET/CT systems, summarizes the performance characteristics for the three different commercially available systems, and reports on the resulting image quality, lesion detectability, and possibilities to reduce scan duration and/or lower the amount of radiotracer administration.

In 2018, the University Medical Center Groningen installed, as the first imaging facility worldwide, the digital SiPM-based Biograph Vision PET/CT (Siemens Healthineers). Therefore, **Chapter 3** evaluates PET/CT system performance conform the NEMA NU 2-2012 standard (61) with additional measurements described in the (at the time of study still unpublished) NEMA NU 2-2018 standard (62). Measurements were directly compared to results from its analog predecessor, the PMT-based Biograph mCT PET/CT (Siemens Healthineers), using existing literature.

Chapter 4 continues on the work described in the previous chapter evaluating initial clinical experiences with the digital Biograph Vision PET/CT in terms of perceived image quality and semi-quantitative analysis in comparison with the Biograph mCT. To this aim, 20 oncological patients underwent a dual ^{18}F-FDG PET/CT imaging protocol including a scan on both systems. Images were blindly reviewed by three nuclear medicine physicians, and semiquantitative analysis was performed on lesions and healthy tissues for comparison between systems.

Progressing on the foregoing chapter, **Chapter 5** aims to evaluate the effects of reduced scan duration in oncological ^{18}F-FDG PET imaging on semiquantitative and subjective imaging parameters and its influence on clinical image reading. For this study, 30 patients underwent a 180 seconds per bed/position listmode PET acquisition which were subsequently reprocessed into additional images obtained with shorter scan durations. Semiquantitative lesion and healthy tissue uptake measurements were performed on each of the reconstructed images and image quality was visually evaluated by three nuclear medicine physicians.

Chapter 6 focuses on image quality and activity optimization using ^{89}Zr labeled mAb PET tracers. The difference in semiquantitative performance between the Biograph mCT and the Biograph Vision PET/CT was investigated. Hereto, 5 patients underwent immunoPET imaging on both systems and images were semi quantitatively analyzed through segmentation of tumor lesion(s) and healthy tissues. Furthermore, the effects of reducing scan duration using the Biograph Vision PET/CT on semiquantitative imaging parameters and its influence on visual image quality assessment were evaluated. Listmode PET data obtained from 15 patients, which were subsequently reprocessed to obtain images at shorter scan durations, were semiquantitatively analyzed and image quality was visually evaluated by three nuclear medicine physicians.

In 2021, the University Medical Center Groningen installed the LAFOV Biograph Vision Quadra PET/CT system (Siemens Healthineers). To provide the nuclear medicine field with a first impression of the improved image quality obtained with such a high-sensitivity system, **Chapter 7** showcases ^{89}Zr immunoPET images of two patients obtained with the Biograph Vision Quadra PET/CT. For a complete overview, and a direct comparison of image quality, these two patients underwent a dual imaging protocol including one scan on the LAFOV Biograph Vision Quadra and the other scan on either the conventional analog Biograph mCT or digital Biograph Vision PET/CT system.

To test the new LAFOV system's compliance to current EARL standards for ^{18}F-FDG tumor imaging (specified for conventional FOV PET systems) to facilitate multicenter research and harmonized clinical use, **Chapter 8** presents EARL phantom measurements with additional tests at various locations throughout the LAFOV and the use of shorter scan durations. Furthermore, clinical PET data of 10 oncological patients were collected to further explore and validate the effects of reducing scan duration on semiquantitative PET image biomarker accuracy and precision when using EARL-compliant reconstruction settings.

Since quantitative accuracy of SUV can be influenced by changes in plasma kinetics, e.g., due to treatment, and SUV derived from static images cannot distinguish between specific and nonspecific uptake, which are issues that could be overcome by dynamic ^{18}F-FDG whole body (Patlak) imaging, **Chapter 9** focuses on this full quantitative imaging method. This study aims to reduce the total examination time of dynamic ^{18}F-FDG whole body (Patlak) imaging, with data simulations, from up to 75 min to 30-60 min p.i. using a population averaged input function.

Chapter 10 continues on the previous chapter by validating the use of a population-averaged input function to reduce examination time of the dynamic ^{18}F-FDG whole body (Patlak) imaging procedure with dynamic whole body ^{18}F-FDG PET data obtained using the LAFOV Biograph Vision Quadra PET/CT system. To this aim, twelve patients with suspected lung malignancy were included and underwent a 65 min dynamic PET acquisition. Full quantitative Patlak analysis was performed on both the entire 65 min scans, as well as on various shortened scan durations, using a population-averaged input function for comparison.

Chapter 11 provides an overview of potential future research directions, potential developments in photon detection technology, and (more cost-effective) hardware developments in PET detectors.

Chapters 12 and 13 present an English and Dutch summary (Nederlandse samenvatting) of the research described in this thesis, respectively.

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