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New PET technologies

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Chapter 11

Future perspectives and concluding
remarks



Since the 1970's, when the first PET systems were built, there has been a significant evolution in PET system technology. Progress in development of detector technology from photomultiplier tubes (PMTs) to silicon-based photomultiplier (SiPM) detector elements has led to the development of digital PET/CT scanners. Performance, image quality, and implications for clinical practice of this major step in PET technology development have been described in **Chapters 2-6** in this thesis. The latest improvement in PET system technology is the development of long axial field-of-view (LAFOV), or so-called total body, PET/CT systems resulting in a larger simultaneous coverage of the human body and a greatly increased sensitivity (a factor of 10 to 40 depending on the length of the scanner) compared with conventional PET scanners (1,2), illustrated in **Chapter 7** with improved image quality and increased signal-to-noise ratio (SNR) in ^{89}Zr ImmunoPET imaging. **Chapter 8** continues with LAFOV PET imaging and touches upon the first benefits in terms of reduced scan duration or injected radiotracer activity, or both, when using ^{18}F -FDG for oncological applications. Moreover, the large coverage of an LAFOV PET system enables simultaneous dynamic imaging of all internal organs and (possible) tumor lesions (3,4). The current chapter will more elaborately focus on future possibilities using LAFOV PET for clinical and research applications. In addition, possible future hardware developments in PET detectors, new photon detection technologies, and the associated expected benefits in both research and clinical settings will be described.

PET imaging optimization

The ability to determine the position of single annihilation events along the line of response (LOR) with precise timing information (time-of-flight (ToF)) is the strength of state of the art PET systems. With the introduction of digital PET technology, ToF improved to 210-400 picoseconds (ps) thereby providing images with improved quality (5). Moreover, on analog systems the sensitivity was one of the limiting factors in both temporal and spatial image resolution; long acquisition times were applied and image filtering was often used to reduce image noise. The improved sensitivity in state of the art PET systems results in a substantial increase in counts, i.e., detected annihilation photons, which results in improved statistics and thus substantially increased SNR as well (4).

Increased sensitivity of LAFOV PET systems now results in images with low noise and improved underlying anatomic details not easily appreciated on conventional PET systems, including activities related to brain substructures (e.g., basal ganglia subregions (6)) and vessel walls. This improvement in image quality may have direct effect on clinical applications resulting in a better understanding of disease burden and residual disease evaluation (3). Higher system sensitivity and improved ToF mean that diagnostic image quality can be obtained at shorter scan durations or with

less injected activity than is typically used in current clinical practice (3,7).

Imaging with lower radiation exposure

A significant reduction in injected activity results in a proportional reduction in radiation exposure, which enables new applications for ^{18}F -FDG PET. For example, it may become feasible to screen high-risk populations for early detection of malignancies in subjects who have no symptoms (yet), e.g., based on abnormally altered blood biomarkers and/or genetic risk factors.

In oncology, many patients undergo repeat imaging, especially when evaluating treatment response. More frequent response monitoring assessments, and consequently the possibility to swiftly switch to another, more effective treatment is possible with reduction in administered radioactive dose (2,4). In the case of monoclonal antibody (mAb) treatment, lowering the administered radioactive ^{89}Zr dose allows for repeat immunoPET scans.

At present, immunoPET is used almost exclusively in a research setting concerning oncological patients with a relatively shorter life expectancy. High mean effective doses are obtained using ^{89}Zr -labeled mAbs ranging from 0.36-0.66 mSv/MBq (8). Administering a standard 37 MBq of ^{89}Zr activity results in a radiation exposure of up to 25 mSv. Lowering the amount of administered radioactive ^{89}Zr activity could reduce radiation exposure to below 10 mSv which opens up the possibility to use labeled mAbs for other indications, for example, younger patients with inflammatory diseases, first in a research setting, in the future maybe also in a routine clinical setting.

In addition, lower radiation exposure facilitates PET imaging in children, who are considerably more sensitive to the carcinogenic effects of ionizing radiation than adults (9). Pediatric patients, often diagnosed with malignant diseases such as lymphoma, require frequent repeat imaging during treatment (10). What's more is the potential of LAFOV PET to facilitate and improve efficacy of drug development, a process that is known to be cumbersome and expensive (11). A major limitation here, often limiting the number of scans performed during a trial, is the maximum permissible radiation dose (12). LAFOV enables imaging with lower doses, consequently there are less restrictions in the number of scans which provides more flexibility to look at different biological processes with a combination of different tracers (2,4). Such a substantial reduction in radiation exposure even opens up inclusion of healthy volunteers (undergoing repeat PET scans) in clinical drug development trials.

For example, in the cases described above, radiation exposure with serial PET imaging using a LAFOV system can be reduced to such an extent, that CT will be the dose limiting factor. (Serial) low dose CT scans merely used for the purpose of PET attenuation and scatter correction, do not provide additional clinical information.

Hence, more emphasis is placed on developing reconstruction algorithms that do not require a CT for attenuation correction, such as maximum likelihood reconstruction of attenuation and activity (MLAA) (13,14). CT-based PET attenuation correction is the current clinical standard where the attenuation of x-rays transmitted through the patient directly relates to electron density; CT Hounsfield Units undergo (bi-) linear transformation to PET linear attenuation coefficient values resulting in an attenuation map, or μ -map (15). Image quality and quantitative accuracy rely heavily on correction of absorption and scatter caused by photon-tissue interaction of the detected photons; varying electron density and tissue thickness influence photon attenuation which, in some regions, can result in a 90% signal reduction (15,16). MLAA methods for attenuation correction rely primarily on emission data to estimate attenuation information through iterative joint estimation based on maximum likelihood and are promising reconstruction approaches to enhance quantitative accuracy of CT-free PET studies (15,17,18). Other possibilities for ultralow-dose CT acquisition are for example the application of a tin filter (19,20) or a split-filter consisting of a gold and a tin part (21) achieving radiation doses as low as 0.06 mSv for a thoracic CT scan (22). However, the suitability of these filtered CT for accurate PET attenuation correction has not been demonstrated yet.

Low-dose imaging may also enable dual isotope imaging or multiple studies (with different radioactive tracers) in a single patient examination. For example, dual isotope imaging to study two physiological functions with two radioactive tracers simultaneously in a single acquisition, such as simultaneous imaging of tumor hypoxia and metabolism using ^{60}Cu -diacetyl-di(N^4 -methylthiosemicarbazone) co-injected with ^{18}F -FDG (23). Simultaneous study during one acquisition, instead of two separate sessions, will be more comfortable for the patient, will reduce radiation exposure to the patient by requiring only one CT, will reduce the cost, and will avoid inaccuracy due to possible metabolic changes between two separate acquisitions (23).

Faster static PET imaging procedures

Reprocessing of acquired listmode data has shown that diagnostic image quality scans can be obtained using 1-2 min scan duration, or less (1,6,7). Fast PET imaging allows a higher patient throughput, limited by patient positioning time, rather than scan duration. Consequently, more patients could be scanned within a certain time window so that these patients can be studied with the same tracer production batch leading to a reduction in overall costs (please note, in case of faster examination times without lowering the amount of injected activity, a larger tracer production batch is required). Furthermore, a significant reduction in scan duration may make it possible to scan patients who are unable to lay still for a long time, children

(without anesthesia) or elderly patients, and patients, e.g., with severe back pain or claustrophobic patients (4). In the case of Intensive Care Unit patients, in which PET/CT imaging is currently not often performed due to logistical issues and the need for continuous monitoring in unstable patients (24), an ultra-fast scan protocol may be beneficial adding to the anatomical CT in a one-stop shop metabolic information, for example on possible sources and locations of frequently occurring infections.

Other applications of faster PET acquisition procedures can be for example indeterminate pulmonary nodule quantification of ^{18}F -FDG uptake to distinguish benign (i.e., inflammatory processes) from malignant disease. Particularly imaging and quantification of small nodules (<1 cm) (25) at the lung bases is erroneous due to partial volume effects and respiratory motion artifacts (3). Breath-hold ^{18}F -FDG PET, acquiring images in 15-30 seconds, may be achieved with a LAFOV scanner which can mitigate these issues (26) and obviate the necessity to apply sophisticated motion-correction algorithms (27).

Delayed imaging

Equivalent to imaging with lesser injected radioactive tracer, the increased sensitivity of a LAFOV scanner could be used for delayed imaging, with acquisition times post injection (p.i.) far beyond the possibilities of conventional PET systems; for ^{18}F -FDG, e.g., 2-18 hours (10 half-lives) (6,7). This prolonged uptake time ensures increased trapping of the tracer via the hexokinase enzyme in metabolically active tissues. Tumor contrast increases over time and nearly full washout of free (i.e., non-metabolized) ^{18}F -FDG (background) occurs, resulting in a higher lesion-to-background ratio; the signal's specificity increases. Delayed imaging is particularly promising in detecting metastases in tissues with high physiological uptake such as the liver which decreases over time (28). The acquired standardized uptake value (SUV) image at 2-18 hours p.i. could resemble the parametric image of ^{18}F -FDG influx rate (K_i) using simple and easy static imaging and reconstruction without the need for time consuming whole body dynamic image acquisition, reconstruction, and analysis. However, this needs to be explored in future studies.

A prolonged uptake time with long-lived radionuclides, e.g., ^{89}Zr immunoPET imaging, e.g., beyond 7 days, is expected to similarly result in an improved lesion-to-background ratio. Furthermore, combining delayed imaging with novel radioactive agents, including new ^{89}Zr immunotracers, allows extended study of *in vivo* biology (29).

Opportunities in dynamic imaging

The aforementioned semiquantitative SUV of ^{18}F -FDG, derived from static images obtained at 60 minutes p.i., is most commonly used as a surrogate of metabolic

activity for tumor uptake quantification (30). Following standardization methods can mitigate SUV variability to a great extent (30-32), however, cannot account for changes in plasma kinetics and cannot distinguish between specific and nonspecific uptake. This may lead to a dissociation between inaccurate SUV measurements and actual tumor metabolic activity (33-35). Conversely, dynamic PET imaging is able to include this information as it allows spatiotemporal activity concentration measurement, providing voxel-wise metabolic information after applying full kinetic- or Patlak analyses (36-38). **Chapters 9 and 10** in this thesis described a method to reduce the total examination time of dynamic ^{18}F -FDG whole body (Patlak) imaging from up to 75 min to 30-60 min p.i. and 40-60 min p.i., respectively, using a population-averaged input function, making full kinetic- or Patlak analyses more suitable for application in the clinic. The otherwise occupied camera time can, in the case of shortened whole body Patlak imaging, be used for another or maybe two routine clinical static PET examinations.

Non-invasive full quantitative imaging

The higher sensitivity and larger axial coverage of the body allow LAFOV PET to capture time-activity in multiple organs and lesions relatively noise free, which enhances our ability to study the pharmacokinetic behavior of radiotracers. Using conventional PET systems, an image derived input function (IDIF) can only be obtained for studies where the heart or a large blood pool structure is in the (restricted) axial field-of-view (FOV). As LAFOV PET imaging captures the heart together with all other main organs of interest, it ensures the FOV always contains a large vascular structure for an IDIF. Moreover, dynamic total body scans make it possible to derive quantitative biological information for multiple lesions within a single FOV. This is important in those cases where interlesional heterogeneity exists and where static images are non-informative or misleading, such as was seen for ^{11}C -erlotinib (39). Given known associations of tumoral heterogeneity and resistance to targeted therapy, capturing all lesions simultaneously and dynamically is important for response monitoring (40), as overall response depends on the response of the least responsive lesion (4).

For other tracers than, for example ^{18}F -FDG, that are not ‘metabolically trapped’ inside the cell and undergo metabolism, kinetic modeling requires a more complex approach than Patlak analyses taking into account reversible kinetics and/or tracer metabolism. Studying the dynamic tracer uptake in the liver may provide a means to non-invasively estimate tracer metabolism and derive a metabolite corrected plasma input function, although this is yet to be explored.

Human connectome

Unique about a LAFOV system is capturing all relevant organs in one FOV with enhanced pharmacokinetic modeling possibilities which provides a unique means to quantitatively and non-invasively study the physiological or pathophysiological interactions between organs, the human connectome, including brain-body interactions (3).

There is increasing evidence that many diseases, traditionally thought to be limited to a single organ, are involved in complex interplays with other organs or organ systems (41). For example, the brain-gut axis: bacteria in the gut might be linked to a whole family of neurological disorders (41-44). Furthermore, more evidence shows gut-lung crosstalk and herewith the influence of the gut microbiome and gastrointestinal disorders on chronic inflammatory reactions in the airways (45) and treatment response in advanced non-small cell lung cancer (46). Also, the importance of the gut-lung axis in managing Covid-19 diseases has been described, e.g. targeting gut microbiota can avoid progression of Covid-19 (47-50). Here, labeling of immune cells of the gut to follow interactions with distant organ systems could be captured with LAFOV.

It has also become apparent that cardiovascular function, neurochemical asymmetries and depression are interconnected (51). Furthermore, recently, a tight inflammatory interaction has been revealed between the myocardium and the kidneys as secondary affected organs following acute myocardial infarction (52), i.e., the heart-kidney axis. Moreover, the so-called brain-heart axis is for example implicated in cardiovascular complications after acute ischemic stroke known as the stroke-heart syndrome (53).

Future PET developments

Apart from improving detector efficiency and increasing the geometrical acceptance through extension of the axial length of the PET system, there is another way to increase photon detection sensitivity: pushing ToF performance. Improving ToF performance can be combined with enhancement of detector efficiency and extending the axial FOV to further increase PET effective sensitivity (54). Improving ToF PET from the current 200 ps to 10 ps would ultimately allow reconstruction-free imaging, i.e., PET imaging without the need for reconstruction because of the improved spatial resolution along the LOR of less than 1.5 mm (54). The benefits and opportunities of improved sensitivity using LAFOV PET as described above in this chapter would be even more extensive in combination with 10 ps ToF. Cherenkov light detection, a phenomenon described later in this chapter, could also play a role in pushing ToF performance.

Another application of interest could be translating the use of 10 ps ToF PET in the design of LAFOV PET systems, without increasing the cost, using PET sparse-

ring detector configurations (54-56). Previous research demonstrated feasibility of reducing the number of detectors by 50% without compromising image quality compared to a standard conventional FOV PET system (57). With the expected improved spatial resolution along the LOR, the same number of detectors used in conventional PET systems could be used for larger axial coverage (1 - 2 m). The main advantages of such an extended coverage include simultaneous dynamic imaging of all internal organs and (possible) tumor lesions, as described above, however without the relative high cost associated with an LAFOV PET system, at present (54,57).

Furthermore, one focus of PET development is detector technology. Current detector technology incorporates pixelated scintillation crystals which form the dominant factor determining system spatial resolution. Instead of pixelated scintillating crystals, monolithic ones, consisting of a continuous scintillation crystal coupled to an array of SiPMs, which can provide depth-of-interaction (DOI) information, could overcome this limitation in spatial resolution, improve system resolution also at off-center positions using DOI measurement, and maintain high sensitivity (58). Inside the crystal, the incoming scintillation light spreads and the light distribution can be sampled by the SiPM array. From the shape of the light distribution, the 2D position and DOI can be derived. This is especially relevant for LAFOV PET systems, where DOI is of interest to correct for parallax effects and degradation of spatial resolution in the axial direction (58). However, where pixelated crystals are one-to-one coupled to a single photosensor element with no involvement of neighbor photosensors allowing the collection of high amounts of photons in a short time frame, the wide light spread in the monolithic block activating multiple photosensors prohibits the collection of a high number of photons per photosensor element in a short time, which is essential for a good ToF performance (59). For digital SiPM arrays introduced by Philips Digital Photon Counting, the use of multiple time stamps for each scintillation event can overcome this issue and sub-200 ps timing resolution can be achieved (60). For analog SiPM arrays, multichannel application-specific integrated circuit (ASIC)-based readout using the TOFPET2 ASIC (PETsys, Lisbon, Portugal) comes into play (61). This ASIC was designed to operate in different PET light collection schemes such as one-to-one coupling or light-sharing among several SiPM pixels. This is ongoing research and timing resolution for a thick monolithic scintillation block is now down to 580 ps (62).

Continuing on this concept of a continuous scintillation medium, the PETALO (Positron Electron ToF Apparatus using Liquid xenOn) is a prototype PET scanner which uses liquid xenon as the active scintillating material, coupled to UV-sensitive vacuum ultraviolet (VUV)-SiPMs (63), incorporating the TOFPET2 ASIC general

architecture for scintillation readout (61). A promising development in PET detector technology which could play an important role in reducing costs for LAFOV PET systems (64) with liquid xenon costs of around 3 \$/cc (65) compared to 22-30 \$/cc for lutetium oxyorthosilicate (LSO)/lutetium-yttrium oxyorthosilicate (LYSO) crystals (66). As liquid xenon is a continuous medium with uniform response which can be incorporated in a single compact, full-body, and highly efficient detector, the localization of annihilation events is expected to be improved resulting in improved image quality. Monte Carlo characterization shows that this setup can currently achieve a timing resolution of approximately 350 ps and a spatial resolution of 1-2 mm at FWHM (64).

Another development providing a cost-effective solution for LAFOV PET systems is the plastic scintillator alternative for LSO crystals (67). Axially arranged scintillators reduce the costs of readout electronics and SiPMs as well (67). A plastic-based LAFOV PET system is expected to cost about five times less than the crystal-based LAFOV PET system (68). With respect to conventional FOV LSO systems, the plastic-based LAFOV PET system with 200 cm axial coverage results in a 27-fold gain in sensitivity as compared to 46-fold for the 200 cm crystal-based LAFOV PET (68); thus a slight compromise on sensitivity with the benefit of LAFOV opportunities at reduced cost. Furthermore, where in current PET imaging procedures, prompt gammas are generally a source of unwanted background, since the plastic-based PET is not restricted to standard double annihilation photon coincidences, it allows capturing events originating from various isotopes simultaneously (one with a prompt gamma and one without a prompt gamma); i.e., information can be obtained from two tracers (one with a prompt gamma and one without) simultaneously during a single PET examination (68,69).

Moreover, positronium imaging incorporates a detection alternative which is a promising new imaging approach to assess tissue pathology *in vivo* (68). Detection in conventional PET is based on the annihilation of a positron with one of the electrons in the surrounding tissue. The emitted positron can also form the metastable state of an electron and positron called a positronium (70), which may be trapped inside free volumes between and within molecules *in vivo*. Imaging the properties of positronium such as the average lifetime, which depends on the size of free volumes between atoms, correlates with the stage of the development of metabolic disorders and may provide new diagnostic information (70,71). Approximately 40% of annihilations proceed via formation of positronium, whereof 0.5% decay in three photons. Even though the rate of three photon producing annihilations is low, imaging may be feasible with highly sensitive (plastic-based) LAFOV PET systems (70).

Alternatively, Cherenkov light detection is another approach which has been under

development for over a decade (72,73). This phenomenon can be exploited and re-introduce bismuth germanate oxide (BGO) scintillators, towards a more cost-effective ToF-PET detector alternative to LSO/LYSO (4-5-fold lower scintillation material cost) (74). Extraction of improved timing information from the relatively few emitted Cherenkov photons is now feasible because of recent developments in near-ultraviolet high-density (NUV-HD) SiPM technology (75,76). Cherenkov light is produced when an electron travels with enough kinetic energy through scintillating material, faster than the speed of light. When detected, this promptly emitted form of light can be used to estimate 511 keV photon interaction time with improved accuracy than achievable with the overall luminescence yield, hence improving timing resolution (74); the fast rise of the Cherenkov signal can be distinguished from the slower overall luminescence yield with rise time correction signal processing methods. BGO is favored over LSO because of its higher refractive index, producing more Cherenkov light. In addition, BGO allows better transmission of UV light. The study by Gonzalez-Montoro et al. (2022) demonstrates ToF performance values of 163 ± 8 , 224 ± 8 , 266 ± 9 , and 428 ± 8 ps for $3 \times 3 \times 3 \text{ mm}^3$, $3 \times 3 \times 5 \text{ mm}^3$, $3 \times 3 \times 10 \text{ mm}^3$, and $3 \times 3 \times 15 \text{ mm}^3$ BGO crystals, respectively, which is equivalent to the ToF performance of state-of-the art LSO PET/CT systems (77,78).

Because of these upcoming developments, many new designs and applications for LAFOV systems will be introduced. Some developments may result in more affordable LAFOV PET system designs and potentially support a more widespread use.

Concluding remarks

LAFOV PET is a new player in the nuclear medicine and molecular imaging field with many clinical workflows to optimize for patient care and new clinical and (advanced) research possibilities to explore. Future technological developments to optimize PET image quality, new detection approaches involving the formation of positronium and the detection of Cherenkov light, and alternative detector materials to make LAFOV PET systems more affordable have been described in this chapter. But first and foremost, this chapter aimed to provide an overview of the opportunities and hypotheses of what LAFOV PET imaging could bring to the field, and to all other medical fields including various patient populations and conditions for which (low dose) PET/CT imaging could be a gamechanger.

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