First experience in UMCG with LAFOV PET: opportunities & challenges

J. van Sluis, MSc; J.H. van Snick, MSc; W. Noordzij, MD, PhD; A.H. Brouwers, MD, PhD; Prof. R. Boellaard, PhD; Prof. R.A.J.O. Dierckx, MD, PhD; Prof. A.W.J.M. Glaudemans, MD, PhD; Prof. A.A. Lammertsma, PhD; Prof. C. Tsoumpas, PhD; Prof. R.H.J.A. Slart, MD, PhD

Medical Imaging Center, Department of Nuclear Medicine & Molecular Imaging, University Medical Center Groningen

Abstract

One of the first long axial field of view (LAFOV) scanners, the Biograph Vision Quadra PET/CT (Siemens Healthineers), was installed at the University Medical Centre Groningen and this article describes the purchasing considerations for investing in such an expensive PET/CT system, first experience in daily clinical practice, and future clinical and research challenges and opportunities.

Introduction

The most specific and sensitive imaging modality for visualising and measuring human (patho) physiology *in vivo* is PET (1). PET is a firmly established biomedical imaging modality with applications in routine clinical diagnostic imaging, but also in research, including clinical trials (2). The ability to identify the lines of response of annihilation photons traveling in about 180 degrees eliminates the need of physical collimation and strengthens the sensitivity of PET imaging. Additionally, state of the art digital PET/CT systems are able to retrace the position of the annihilation event with good timing precision (around 210 -400 ps (3)). In general, system sensitivity has been a crucial limiting factor for imaging with high temporal resolution. A substantial increase of the measured annihilation photons will result in improved statistics with substantially increased signal-to-noise ratio (4).

The increased sensitivity of LAFOV PET systems results in images with exceptionally lower noise levels and better anatomical details than for conventional PET systems, including brain substructures (basal ganglia subregions (5)) and vessel walls. This improvement in image quality may have direct impact on clinical applications, resulting in better understanding of disease burden and residual disease evaluation (6). Alternatively, the higher system sensitivity means that the same diagnostic image quality can be obtained with shorter scan durations or with lower injected dose than is typically used in current clinical practice (6,7). In addition, the large axial coverage allows for dynamic imaging of an organ of interest together with a large vascular structure, where (in principle) the latter can be used to generate an image derived input function (IDIF) (4).

One of the first LAFOV systems, the 106 cm axial field of view (FOV) Biograph Vision Quadra PET/CT (Siemens Healthineers), was placed at the University Medical Centre Groningen and this article will describe the business case for purchasing such an expensive PET/CT system, first experience in daily clinical practice, and future clinical and research challenges and opportunities.

Purchasing considerations

For many hospitals, investing in an LAFOV PET system is too costly to justify to the board of directors. Hence, a realistic business plan is needed, focusing on the opportunities of LAFOV to substantially increase patient throughput (4). It is important to note that several requirements need to be fulfilled to achieve this high patient throughput: 1) as shorter scan duration can be interchanged with lower injected dose (8), a substantial increase in patient throughput can only be achieved if one accepts only a moderate decrease in administered dose; 2) high patient throughput requires rapid successive tracer injections and the radiochemistry lab should be able to keep up with this higher frequency; 3) for higher patient throughput, more facilities are needed for patient preparation (i.e. sufficient uptake and changing rooms); and 4) enough personnel should be available to prepare patients and acquire scans, and of course physicians to read and report those scans.

At present, replacing conventional systems with a LAFOV PET may be financially difficult for many centres. However, if the demand for patient scans is growing, it will be cheaper to increase scanning capacity by replacing one or more conventional systems with an LAFOV PET scanner than with multiple conventional PET/CT systems. As LAFOV system dimensions are similar as those of a conventional system, an LAFOV scanner will fit in an existing room without the need for refurbishments (4). In addition, although you need more personnel to operate an LAFOV

scanner, it will probably be less than for two conventional scanners.

First clinical experience

Improved image quality

For an initial assessment of the performance of the LAFOV Quadra, paired scans were performed on both the Quadra and a (conventional, short axial field of view) digital Biograph Vision PET/CT (Siemens Healthineers). This comparison showed a substantial improvement in image quality, i.e. a higher signal-to-noise ratio (SNR). Examples of acquired patient images are shown in figures 1, 2, 3 and 4.

Reduced scan duration

The next step was to investigate to what extent a reduction in scan duration (equivalent to a proportional reduction in injected dose) would still result in adequate diagnostic image quality. Example patient images for different scan durations are shown in figures 3, 4 and 5.

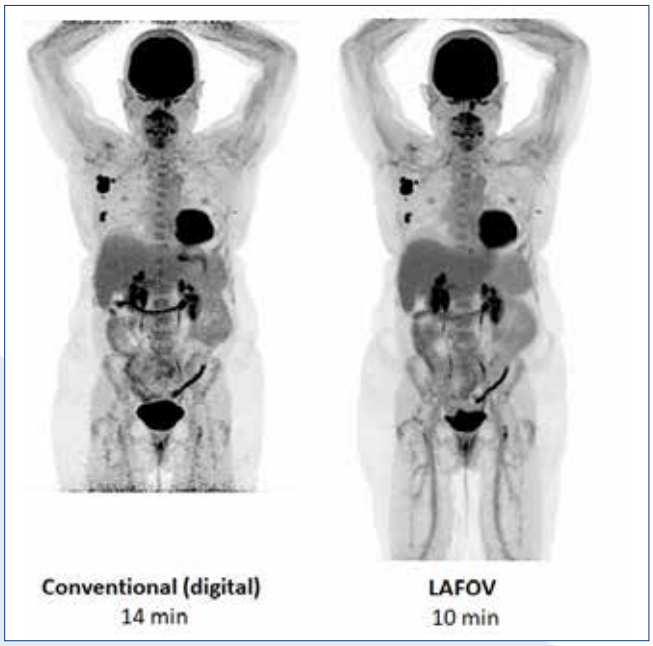

Figure 1. Whole body maximum intensity projection images of a 65 year old female patient with metastatic breast cancer who received an intravenous injection of 200 MBq [^{18}F]FDG. Images were obtained with a total scan duration of 10 min. using the LAFOV Biograph Vision Quadra PET/CT. Subsequently, images were obtained with an acquisition time of approximately 14 min on the conventional digital Biograph Vision PET/CT. Images on the Vision were acquired at approximately 60 min. post injection, whereas images on the Vision were obtained 19 min. later in time. No Gaussian smoothing was applied during reconstruction of these images.

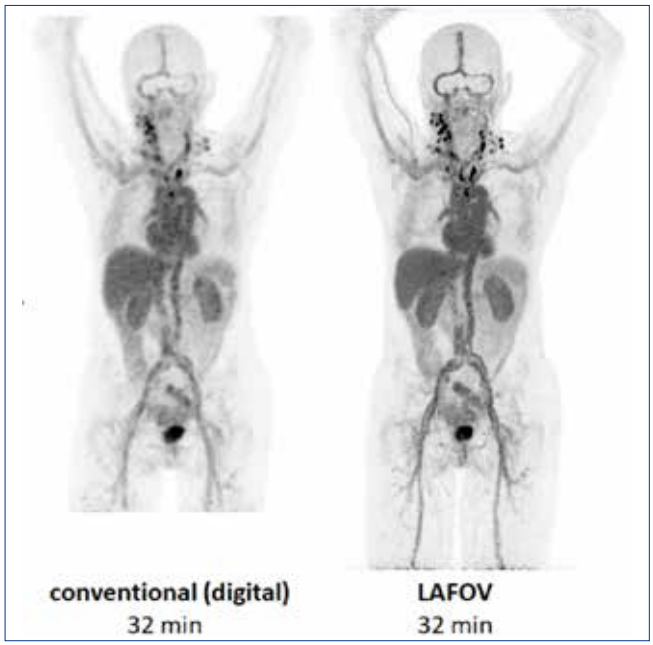

Figure 2. Whole body maximum intensity projection images of a 71 year old female patient with metastatic breast cancer who received an intravenous injection of 37 MBq [^{89}Zr]trastuzumab. Images were obtained with a total scan duration of 32 min. on both the conventional digital Biograph Vision PET/CT (left) and the LAFOV Biograph Vision Quadra PET/CT (right). Scans on both systems were acquired at 4 days post injection. A 7 mm Gaussian smoothing filter was applied to the images obtained on the Vision to reduce noise levels, whereas no smoothing was applied to the images obtained on the Quadra. Images were adapted from (9).

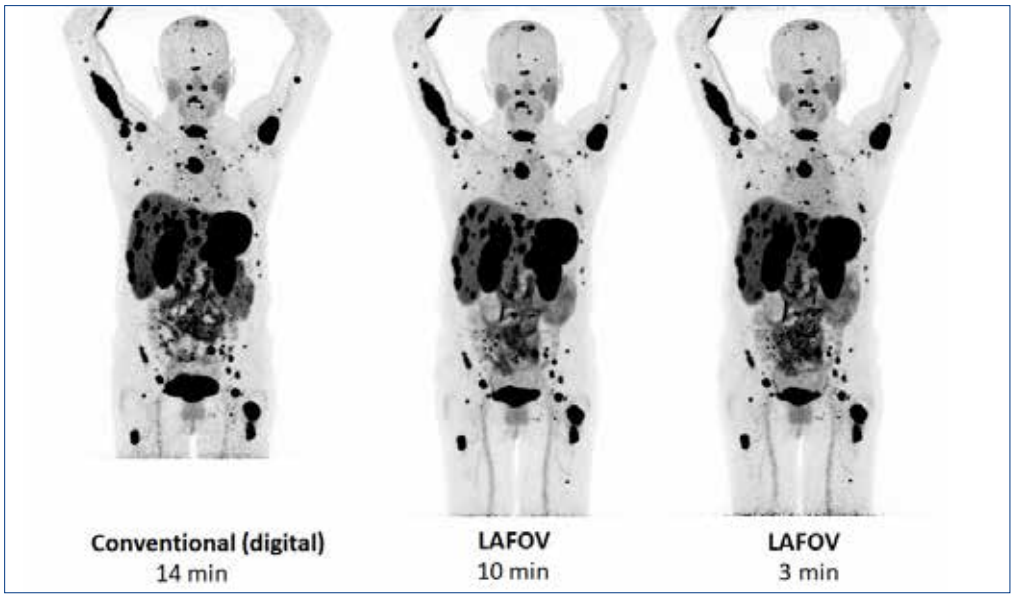

Figure 3. Whole body maximum intensity projection images of a 66 year old female patient with a metastasised neuroendocrine tumour who received a 115 MBq intravenous injection of [^{68}Ga]DOTATOC together with 80 mL intravenous contrast. Images were acquired using a total scan duration of approximately 14 min. using the conventional digital Biograph Vision PET/CT (left) and, using the LAFOV Biograph Vision Quadra PET/CT, total scan durations of 10 (middle) and 3 (right) min. Images on the Quadra were acquired at approximately 60 min. post injection, subsequently images on the Vision were obtained 20 min. later in time. No Gaussian smoothing was applied during reconstruction of these images.

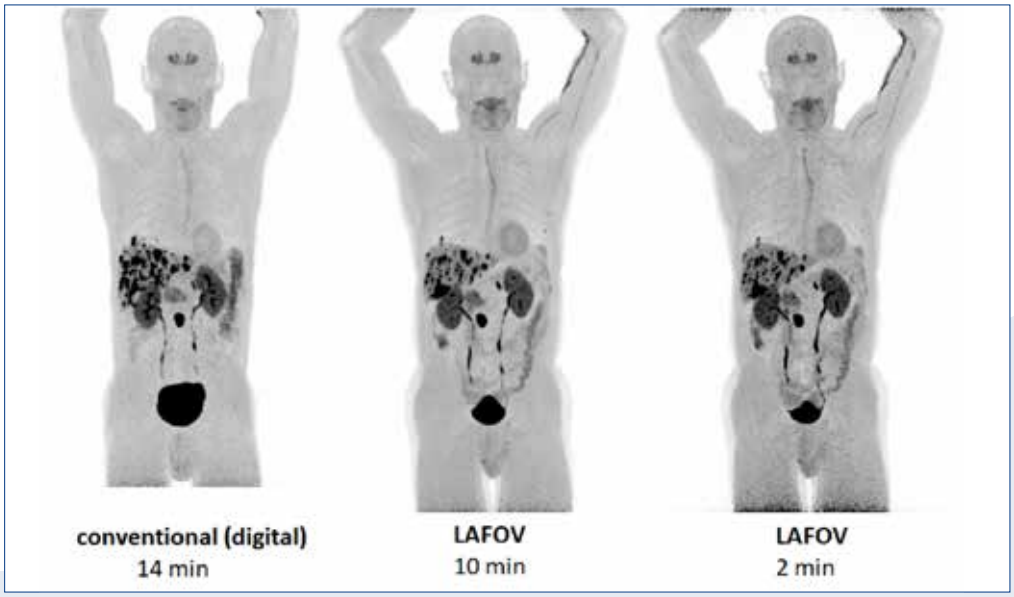

Figure 4. Whole body maximum intensity projection images of a 64 year old male patient with a metastasised neuroendocrine tumour who received a 220 MBq intravenous injection of [^{18}F]F-DOPA together with 150 mg oral carbidopa. Images were obtained with a total scan duration of approximately 14 min. using the conventional digital Biograph Vision PET/CT (left) and, using the LAFOV Biograph Vision Quadra PET/CT, total scan durations of 10 (middle) and 2 (right) min. Images on the Quadra were acquired at approximately 60 min. post injection, subsequently images on the Vision were obtained 21 min. later in time. No Gaussian smoothing was applied during reconstruction of these images.

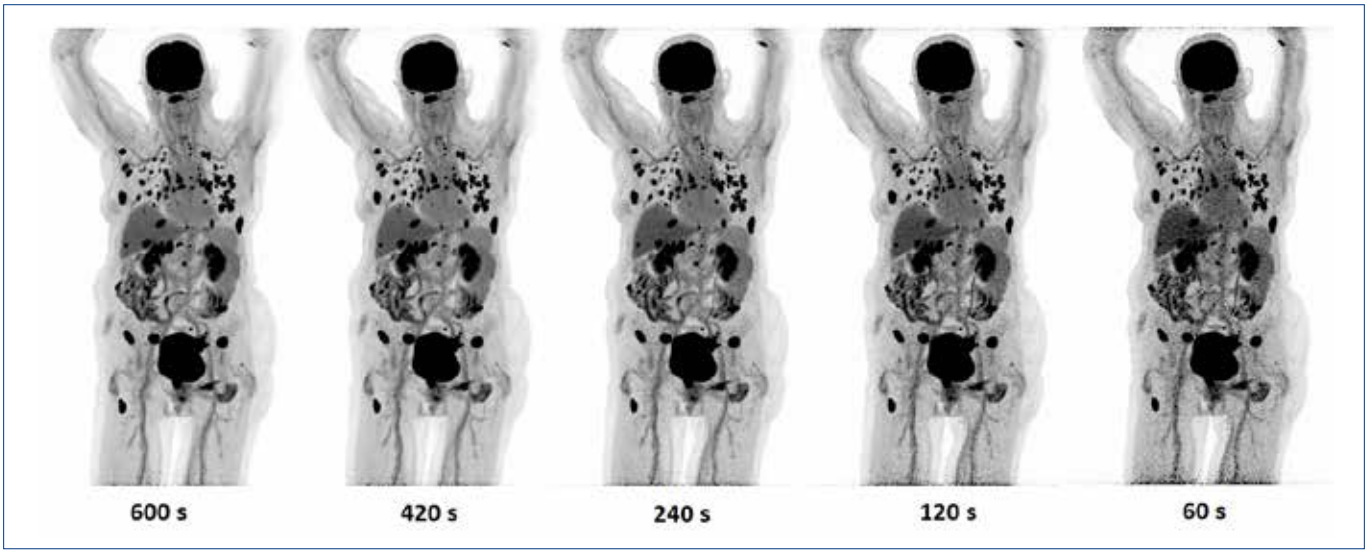

Figure 5. Maximum intensity projection images of an 85 year old female patient with metastatic breast cancer who received a weight-based (81 kg) injection of 240 MBq [^{18}F]FDG activity and underwent a single LAFOV Quadra PET/CT scan of 10 min. Scans were acquired in listmode at 60 min. post injection and reprocessed to reconstruct additional images for shorter scan durations. No Gaussian smoothing was applied during reconstruction of these images.

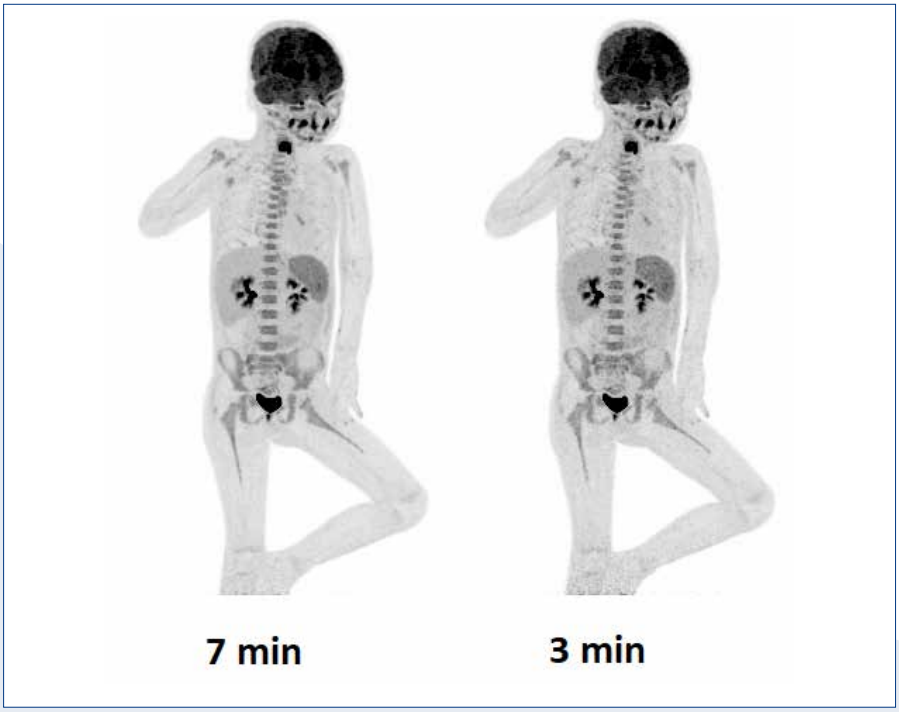

Figure 6. Maximum intensity projection images of a 5 year old female patient with endocarditis who received a weight-based (17 kg) injection of 28 MBq [^{18}F]FDG activity and underwent a single LAFOV Quadra PET/CT scan of 7 min. Scans were acquired in listmode at approximately 60 min. post injection and reprocessed to reconstruct additional images at shorter scan durations. No Gaussian smoothing was applied during reconstruction of these images.

These initial examinations indicated that scan duration can be reduced to approximately 2 min for adequate diagnostic image quality using an optimised clinical reconstruction protocol without applying Gaussian smoothing. When additional Gaussian smoothing is applied during reconstruction, even shorter acquisition times could be used. It should be noted that, instead of reducing scan time, the injected tracer dose could have been lowered to the same extent, which opens up possibilities in for example paediatric care (see figure 6). The shorter scan time, still producing adequate image quality, indicates that a reduction of the dose with at least a factor 2 for future paediatric examinations is feasible.

Future clinical and research opportunities and challenges

Apart from the obvious increase in image quality, faster scan protocols, and imaging with lower radiation exposure, there are many more opportunities in both daily clinical practice and research.

Lower radiation exposure
The significant reduction in injected dose that is possible may enable screening of high-risk populations for abnormal cells that may become cancerous in subjects who have no symptoms (yet).
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 therapy, thereby providing the possibility of more effective treatment is possible due to a reduction in administered tracer dose (4,10). In particular in the case of monoclonal antibody (mAb) treatment, lowering the administered ^{89}Zr dose allows for repeat immunoPET scans for improved follow-up on treatment.

At present, immunoPET is used almost exclusively in oncological patients with a relatively short life expectancy. By reducing radiation exposure through lowering the amount of administered ^{89}Zr, it becomes possible to use labelled mAbs for other indications, such as younger patients with inflammatory diseases.
In addition, lower radiation exposure facilitates PET imaging of children, who are considerably more sensitive to the carcinogenic effects of ionising radiation than adults (11). PET imaging using an LAFOV system can be reduced to such an extent, that the CT dose will be the dose limiting factor. Hence, more emphasis will be placed on using ultra low dose CT scans and on developing reconstruction algorithms that do not require a CT scan for attenuation correction.
LAFOV PET also has the potential to facilitate and improve efficacy of drug development, a process that is known to be cumbersome and expensive (12). A major limitation, often limiting the number of scans performed during a trial, is the maximum permissible radiation dose. LAFOV PET enables imaging with lower doses, resulting in less restrictions in the number of scans, which in turn provides more flexibility to assess various biological processes with a combination of different tracers (4,10). Such a substantial reduction in radiation exposure may even allow inclusion of healthy volunteers in clinical drug development trials.

Delayed imaging
Equivalent to imaging with less injected radioactivity, the increased sensitivity of an LAFOV scanner could also be used for delayed imaging, i.e. with acquisition times post injection that are far beyond the possibilities of conventional PET systems. For example, for [^{18}F]FDG, imaging could be performed anytime within the 2-24 hours post injection window (5,7). This prolonged uptake time ensures more complete trapping of the tracer via the hexokinase enzyme in metabolically active tissues. Tumour contrast increases over time and nearly full washout of free (i.e. non-metabolized background) [^{18}F]FDG occurs, resulting in a higher lesion-to-background ratio. Delayed imaging is particularly promising in detecting metastases in tissues with high physiological uptake such as the liver, where prolonged clearance may be helpful (13). For semi-quantitative purposes, the acquired standardised uptake value (SUV) image at later times will better resemble a parametric image of the [^{18}F]FDG net influx rate constant (K_i), thereby potentially obviating the need for time consuming whole body dynamic image acquisitions.
A prolonged uptake time with long-lived radionuclides, such as ^{89}Zr-labelled mAbs, 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-labelled tracers, will allow the study of biological processes over a longer period of time (14).

Dynamic imaging
The aforementioned semi-quantitative SUV of [^{18}F]FDG, derived from static images obtained at 60 minutes post injection, is commonly used as a surrogate of tumour metabolic activity (15). Although standardisation methods can mitigate SUV variability to a great extent (15-17), they cannot account for changes in plasma kinetics and cannot distinguish between specific and non-specific uptake which may lead to a dissociation between SUV measurements and actual tumour metabolic activity (18-20). In contrast, dynamic PET imaging is able to include this information as it allows spatiotemporal activity concentration measurements, providing voxel-wise metabolic information after applying full kinetic or Patlak analyses (21-23). The higher sensitivity and larger axial coverage of the body allows LAFOV PET to capture relatively noise free time-activity curves in multiple organs and lesions, which enhances the ability to study pharmacokinetic behaviour of the radiotracers. Using conventional PET systems, an image derived input function (IDIF) can only be obtained for studies where the heart is in the (restricted) 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 (4). In addition, the inclusion of the liver may provide a means to non-invasively correct an IDIF for labelled metabolites.
Most importantly, dynamic total body scans make it possible to derive quantitative biological information for multiple lesions. This is important in those cases where interlesional heterogeneity exists and where static images are non-informative or misleading, such as for ^{11}C-erlotinib (24). Given known associations of tumour heterogeneity with resistance to targeted therapy, capturing all lesions simultaneously is important for response monitoring (25), as overall

Table 1. Overview of opportunities and challenges of an LAFOV PET/CT scanner. Adapted from (4)

Opportunities	**Challenges**
<u>Improved image quality because of increased sensitivity</u> • No need for smoothing, therefore maintenance of high spatial resolution • Ability to reconstruct at smaller voxel size, allowing high spatial resolution • Detect low-grade uptake • Detect disease at earlier stage • Delayed imaging for imaging slower biological processes (e.g. immunotherapy)	• Amend PET image standardisation and harmonisation protocols
<u>Shorter scan duration</u> • High patient throughput • Scan ICU patients • Scan paediatric patients (possibly) without anaesthesia • Increase patient comfort and compliance	• More patient preparation facilities needed • More staff needed for patient care and image reading (not if the scanner replaces 2 or more conventional scanners) • Radiochemistry lab should be able to handle increased successive activity injections
<u>Dose reduction</u> • Imaging radiosensitive populations (paediatrics, pregnant women, etc.) • More frequent imaging for improved therapy response evaluation • Dual tracer imaging • Wider acceptance for use in clinical trials • Possibility of including healthy volunteers in clinical trials • Use of labelled monoclonal antibodies for other indications than oncology	• Still attenuation correction using CT, therefore CT will become the dose-limiting factor
<u>Imaging kinetics with greater temporal range</u> • Image faster biological processes because of higher temporal sampling • Image slower biological processes because of the ability to scan over a longer period of time • Derive an image derived input function with higher accuracy • Extract more valuable information from one scan	• Requires metabolite correction for tracers other than 18F-FDG • Slow computational times for reconstruction and complex kinetic modelling
<u>Imaging with a longer axial view</u> • Imaging multiple organ systems (e.g. organ axes) and/or lesions simultaneously (important in case of interlesional heterogeneity) • Presence of a large vascular structure in the FOV for obtaining an image derived input function	• Obtaining blood samples is difficult because accessible arteries are hard to reach • Expensive with regard to conventional PET • Claustrophobic patients will be less compliant • If it replaces multiple conventional scanners, there will be no back-up scanner in case of a breakdown

response depends on the response of the poorest lesion (4).
Typically, a whole body dynamic [^{18}F] FDG PET acquisition procedure can take a total examination time of up to 75 min. (26), including patient positioning and CT scanning, which makes the procedure time-consuming and logistically less attractive and feasible for daily clinical application. Previous work suggests that use of a population-averaged input function could be a good strategy to obtain accurate Ki estimates at a scan time interval of 30-60 min. post injection, making whole-body Patlak imaging more clinically feasible (27). The increased sensitivity of LAFOV PET could allow even shorter scan time intervals post injection.

Human connectome

Unique about an LAFOV system is capturing all relevant organs in one FOV with enhanced pharmacokinetic modelling possibilities, providing a unique means to quantitatively and non-invasively study physiological or pathophysiological interactions between organs and the human connectome, including brain-body interactions (6).
There is increasing evidence that many diseases, traditionally thought to be limited to a single organ, may in fact be the result of disturbances in the complex interplay between organs or organ systems (28). For example, with respect to the so-called brain-gut axis, it is now thought that bacteria in the gut may be linked to a whole family of neurological disorders (28-31). Furthermore, more evidence shows gut-lung crosstalk and herewith the effects of the gut microbiome and gastrointestinal disorders on chronic inflammatory reactions in the airways (32) and even treatment response in advanced non-small cell lung cancer (33). Finally, the importance of the gut-lung axis in managing COVID-19 diseases has been described. For example, targeting gut microbiota can avoid progression of COVID-19 (34-37). Here, labelling 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 (38). Furthermore, the so-called brain-heart axis is implicated in cardiovascular complications after acute ischemic stroke, known as the stroke-heart syndrome (39).

Challenges

The use of an LAFOV PET/CT system provides many opportunities as described above, but it also poses challenges. A full overview of opportunities and challenges is provided in table 1 (4). As mentioned earlier, the most prominent challenge for clinical practice is the need for more uptake rooms to facilitate increased patient throughput. Other more technical/physical challenges are that standardisation and harmonisation guidelines, developed for conventional FOV systems, need to be amended for LAFOV. In addition, claustrophobic patients will find an LAFOV system more challenging than a conventional scanner. Finally, in case an LAFOV scanner has replaced several (two or more) conventional scanners, there may not be a back-up scanning option when it breaks down.

Conclusion

LAFOV PET is the newest addition to the (molecular) imaging armamentarium. It provides many unique opportunities that were not available before, e.g. improved image quality, opportunities to substantially reduce dose and/or scan duration, improved accuracy in monitoring and predicting treatment response, and a means to study molecular interactions between organs. It is expected that this generation of scanners will significantly advance the field of molecular imaging in the near future, and it could become the new standard in the not too distant future.

r.h.j.a.slart@umcg.nl ♦

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