Towards clinical implementation of quantitative PET and SPECT imaging

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CHAPTER 7

Summary, General Discussion and Future Perspectives

SUMMARY

Quantitative positron emission tomography (PET) and Single Photon Emission Computed Tomography (SPECT) have made significant advancements in recent decades and are now incorporated into several clinical guidelines. However, there is considerable potential for their broader application across other indications, indicating that current capabilities are underutilized. A key barrier is the lack of robust evidence, underscoring the need for further research to validate their expanded applications, which could enable personalized treatment plans and improve outcomes across a broader range of diseases.

The aim of this thesis was 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.

Part 1: Novel clinical applications of quantitative PET/CT

Rubidium-82 PET/computed tomography ([^{82}Rb]Cl PET/CT) is increasingly being used for cardiac perfusion imaging. The flow tracer ^{82}Rb accumulates in the myocardial cells, has a short physical half-life (75 s) and a high first-pass extraction in the kidneys that also enables renal perfusion quantification, but is not yet used for this application in clinical practice. **Chapter 2** investigated 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. Our study demonstrated that obtaining renal K_1 and renal blood flow (RBF) values using [^{82}Rb]Cl PET/CT was feasible using a one-tissue compartment model. Applying iso-contouring as the PET-based volumes of interest (VOI) of the kidney and using abdominal aorta (AA) as an image-derived input functions (IDIFs) is suggested for consideration in further studies. Dynamic [^{82}Rb]Cl PET/CT imaging showed significant differences in renal hemodynamics in rest compared to pharmacological stress using adenosine. This indicates that dynamic [^{82}Rb]Cl PET/CT has potential to detect differences in renal hemodynamics in stress conditions compared to the resting state, and might be useful as a novel diagnostic tool for assessing renal perfusion.

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. As more and more patients emerge with long COVID who have symptoms of fatigue, myalgia and joint pain, we must examine potential biomarkers to find quantifiable parameters to define the underlying mechanisms and enable response monitoring. **Chapter 3** assessed the potential added value of non-metabolizable glucose analogue 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG)-PET/CT for long COVID patients. Two analyses were performed: semi-

quantitative analysis using target-to-background ratios (TBRs) in 24 targets and total vascular score (TVS) assessed by two independent nuclear medicine physicians. The targets included nine research targets described in the European Association for Nuclear Medicine (EANM) recommendations for [^{18}F]FDG-PET/CT imaging in large vessel vasculitis and polymyalgia rheumatica: the carotid, subclavia, axillary, vertebral, and pulmonary arteries, the ascending, descending, and abdominal aorta, and the aortic arch. Additional targets consisted of the parotid glands, external iliac arteries, femoral arteries, tibial arteries, the liver and the brachioradialis muscle. Thirteen patients were included in the long COVID group and 25 patients were included in the control group. No significant differences ($P < 0.05$) were found between the long COVID group and the control group in the TBR or TVS assessment. As we found no quantitative difference in the TBR or TVS between long COVID patients and controls, we are unable to prove that [^{18}F]FDG is of added value for long COVID patients with symptoms of myalgia or joint pain. Given that a similar study showed contradicting results, this suggests that more research is needed to understand the underlying mechanisms of long COVID. Nevertheless, these studies, even with negative results, contribute to the growing knowledge of [^{18}F]FDG-PET/CT's application in long COVID.

Chapter 4 assessed 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). $EARL_1$ and $EARL_2$ compliance of the digital-BGO system (Omni Legend 32 cm) was tested for several reconstructions, including those that apply precision deep learning-based image enhancement (PDL) as postprocessing, using the calibration QC and National Electric Manufacturer's Association (NEMA) IEC phantom measurements. When we applied 1 min per bed position for PET acquisition, [^{18}F]FDG administration can be reduced by a factor of ~4 for $EARL_1$, by a factor of ~8 for $EARL_2$ (2 mm voxels) and by a factor of ~4 for $EARL_2$ (4 mm voxels) using both standard reconstructions and PDL post-processing compared to current EANM recommendations for [^{18}F]FDG administration (7 MBq·min·bed^{-1}·kg^{-1}). With this study we provided an initial insight into the applicable lower limit in [^{18}F]FDG administered activity and/or scan time reduction while being $EARL_1$ and $EARL_2$ Fluorine-18 compliant for the Omni Legend PET/CT system. This might allow for a higher patient throughput and/or lower radiopharmaceutical activity, reducing costs and radiation exposure for both patients and staff, while potentially expanding the applications of (quantitative) PET.

Part 2: Novel clinical applications of quantitative SPECT/CT

Myocardial perfusion scintigraphy is based on visual interpretation of relative myocardial perfusion and might underestimate the severity of ischemia due to global hypoperfusion (triple vessel disease). Hence, quantitative SPECT may enable measurement of myocardial

uptake to improve evaluation of response to anti-ischemic therapies using myocardial perfusion scans. **Chapter 5** investigated the quantitative accuracy and precision of a novel iterative reconstruction technique (Evolution; GE Healthcare) for the potential application of response monitoring using [^{99m}Tc]Tc-tetrofosmin SPECT/CT in patients with coronary artery disease (CAD). Our phantom study showed that seven iterations (10 subsets) and Butterworth post-filtering (cut off frequency 0.52in cycles/cm, order of 5) were considered optimal for reconstruction based on convergence and noise level. Applying these settings, the average repeatability deviation (or precision) of all acquisitions was 2.91%. Moreover, the accuracy of Evolution using larger defects resulted in higher recovery coefficients (ranging from 0.64 to 0.75) compared to smaller defects (recovery coefficients ranging from 0.52 to 0.74). To illustrate the feasibility of clinical application, ten patients, before and after intramyocardial injection of autologous bone marrow cells, were included retrospectively. Eight out of ten patients showed significant changes in uptake before and after treatment ($p < 0.05$). This was the first study to evaluate Evolution for cardiac applications demonstrating promising results for the application of quantitative SPECT in patients with CAD.

Molecular Breast Imaging (MBI) is a non-invasive technique for in vivo characterization of breast lesions. It uses the radiopharmaceutical [^{99m}Tc]Tc-sestamibi, a P-glycoprotein (Pgp) substrate, enabling potential prediction of chemoresistance based on uptake levels. Reduced uptake may indicate Pgp overexpression, aiding in prediction of response to neoadjuvant chemotherapy (NAC). Hence, quantification of [^{99m}Tc]Tc-sestamibi accumulation might help guiding treatment decisions. However, recent studies highlight limitations of planar MBI in accurately quantifying tumor uptake, suggesting that SPECT/CT may help overcome these shortcomings. Moreover, prone hanging breast SPECT is a technique in which the patient is positioned face-down (prone) during image acquisition to reduce attenuation and motion artifacts. **Chapter 6** evaluated the semi-quantitative SPECT parameters of prone hanging breast SPECT using [^{99m}Tc]Tc-sestamibi and compared them with MBI-derived semi-quantitative parameters for the potential use of response prediction in women with locally advanced breast cancer (LABC). Eighteen patients with proven LABC with a tumor≥2 cm diameter on mammography and an indication for MBI using [^{99m}Tc]Tc-sestamibi were prospectively enrolled. Various semi-quantitative parameters were composed for early and delayed SPECT acquisitions (5 min p.i and 90 min p.i.) and MBI. No significant difference was observed between MBI and early SPECT semi-quantitative parameter functional tumor volume (FTV) ($p = 0.46$). TBR_{mean} and TBR_{max} were significantly higher for SPECT compared to MBI and showed greater variability between the measurements ($p<0.05$). Moreover, wash-out rates (WOR) showed a large interquartile range (IQR) (62.28), indicating that there is WOR variation among the LABC patients. Also, the FTV derived from early prone hanging breast SPECT/

CT is comparable with MBI-based FTV (p = 0.46). This was the first feasibility study evaluating the semi-quantitative parameters of prone hanging breast SPECT/CT using [^{99m}Tc]Tc-sestamibi and comparing them with MBI-based semi-quantitative parameters in 18 patients with LABC. This study presented the first step towards a possible application of semi-quantitative parameters of prone hanging breast SPECT/CT in LABC patients for prediction of response to NAC.

In conclusion, while extensive technological capabilities for quantitative PET and SPECT exist, their broader clinical implementation is hindered by the slow accumulation of sufficient clinical evidence for new clinical applications. Although effective in established areas (e.g. quantification of myocardial perfusion, patient stratification (theranostics), therapy response prediction), further research is essential to validate their expanded clinical use. Closing the evidence gap will enable these technologies to guide more personalized treatments and improve clinical outcomes. This thesis contributes by exploring novel quantitative PET and SPECT applications in the fields of infectiology, nephrology, oncology and cardiology, but much work remains. Further research is required to optimize quantitative SPECT and PET, thereby enabling a broader patient population to benefit from their full clinical potential.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

The shift towards quantitative evaluation in nuclear medicine represents a significant advancement in diagnostic imaging, offering objective and reproducible data that enhance diagnostic accuracy and might improve patient management. Quantitative PET and SPECT imaging provide valuable insights into physiological and metabolic processes, including the monitoring of disease progression or the determination of therapeutic response. Rapid improvements in nuclear medicine innovations, as advancements in hardware and software, are paving the way for broader adoption of quantitative imaging in routine clinical practice. Moreover, improved temporal resolution in dynamic acquisition makes quantification possible and helps facilitate its adoption in clinical practice. The existing capabilities of quantitative PET and SPECT remain underutilized, as they have not been widely implemented beyond standard fields due to insufficient or inadequate evidence.

This thesis investigates the potential of quantitative PET and SPECT beyond their current applications, focusing on indications where they are not yet applied in clinical practice. This may serve as a foundation for broader integration of quantitative PET and SPECT into clinical practice and eventually contribute to improved patient outcomes through more objective, standardized and less observer dependent diagnostic and therapeutic strategies.

Quantitative dynamic PET for assessing renal perfusion

Chapter 2 applies kinetic modeling to explore the potential use of dynamic [^{82}Rb]Cl PET/CT for assessing renal perfusion. While these techniques are well-established for myocardial perfusion, their application to renal studies remains largely uninvestigated. Despite available software for cardiac imaging, adapting it for renal imaging requires special modifications related to anatomical and physiological differences that are specific for the kidney. In **Chapter 2**, we demonstrated the feasibility of using dynamic [^{82}Rb]Cl PET/CT for determining renal hemodynamics during different physiological conditions (e.g. rest and exposure to vasodilatation by adenosine). Future, larger studies are needed to refine renal dynamic PET protocols including acquisition and processing methods (e.g. VOI delineation), as well as to determine reference values and values in specific patient groups (e.g. high stage chronic kidney disease (CKD), renal artery stenosis). Despite their vital role in overall health, the kidneys are often overlooked in research. As a result, renal diseases are frequently diagnosed at a relatively late stage, contributing to significant morbidity, mortality, and substantial healthcare and societal costs. This underscores the urgent need for greater awareness and further development of diagnostic imaging tools, such as quantitative dynamic PET/CT, that can support earlier detection and intervention in renal disease.

Dynamic PET quantifies renal perfusion by tracking radiotracer distribution over time, enabling the assessment of tracer kinetics in different renal compartments. Among available PET tracers, [^{15}O]H_2O, [^{13}N]ammonia and [^{18}F]Flurpiridaz enable measurement of tissue perfusion due to their high extraction fractions and favorable kinetics. However, [^{15}O]H_2O and [^{13}N]ammonia require an on-site cyclotron for production and their use remains largely preclinical with limited clinical validation to date [1, 2]. [^{18}F]Flurpiridaz is a novel [^{18}F]-labeled PET tracer for myocardial perfusion imaging (MPI), recently approved by the FDA for clinical use. Its relatively long half-life allows production as a unit dose at a regional cyclotron. To the best of our knowledge, no studies have reported its use in renal perfusion imaging [3, 4]. The generator-produced tracer [^{82}Rb]Cl offers greater accessibility and logistical advantages, making it a practical option for renal perfusion imaging, although its lower extraction and short half-life may limit quantitative accuracy.

Other imaging modalities have notable limitations. Ultrasound Doppler provides only qualitative or semi-quantitative flow data, while contrast-enhanced CT and Magnetic Resonance Imaging (MRI) may be limited by nephrotoxicity or low temporal resolution. In contrast, dynamic PET yields absolute perfusion values in milliliters per minute per gram of tissue. This might be advantageous in complex clinical areas such as high stage CKD, renovascular stenosis and monitoring transplant viability. Nonetheless, its ability to provide reproducible quantification across renal compartments positions dynamic PET as a promising tool, potentially bridging the gap between functional imaging and personalized nephrological care.

(Semi)quantitative PET in long COVID

The emergence of new diseases like COVID in 2019 highlights the need for (imaging) biomarkers to identify quantifiable parameters that define underlying mechanisms, assess disease activity, and monitor treatment response. We were unable to demonstrate that [^{18}F]FDG offers added value for long COVID patients with symptoms of myalgia or joint pain (**Chapter 3**). However, no guidelines for interpretation, acquisition and processing exist for [^{18}F]FDG-PET/CT in long COVID patients, aside from the recommendations that come closest to addressing this issue, as outlined in **Chapter 3**.

Long COVID is a complex post-viral condition involving persistent symptoms, inflammation, and immune dysregulation. [^{18}F]FDG-PET/CT offers significant value in early detection of infection and inflammation by identifying subtle metabolic abnormalities, with superior sensitivity to anatomical imaging techniques like chest X-ray, CT, and MRI. Furthermore, [^{18}F]FDG-PET/CT allows semi-quantitative assessment of inflammation and recovery, using standardized uptake values [5]. In long COVID, quantitative PET holds significant potential to substantially improve patient stratification, reveal key pathophysiological mechanisms,

such as neuroinflammation or pulmonary inflammation, and enable effective monitoring of treatment [5, 6]. However, several challenges remain, including the lack of validated disease-specific thresholds and the considerable clinical and biological heterogeneity of long COVID. Patients show a wide spectrum of symptoms affecting multiple organ systems, with underlying mechanisms varying from persistent inflammation and immune dysregulation to microvascular injury and autonomic dysfunction. This variability complicates the interpretation of medical imaging (also PET) findings and underscores the need for tailored (quantitative) imaging protocols to accurately capture the pathological variations within the long COVID population.

Moreover, emerging evidence suggests that brain [^{18}F]FDG-PET provides valuable insights into the neurological effects of long COVID, since it has revealed a characteristic hypometabolic pattern in the brain in a substantial proportion of individuals with long COVID, suggesting the involvement of specific neural networks. As such, it may serve to objectively confirm brain involvement and support differential diagnosis against neurodegenerative, inflammatory, or psychiatric conditions [6]. (Semi)quantitative analysis enhances visual assessment, especially for less experienced readers, by utilizing an age-matched control database and a PET system with comparable (i.e. harmonized) performance characteristics, thus providing more reliable and objective results [7].

Further research and standardization are needed before PET/CT becomes part of routine clinical use in long COVID patients. Furthermore, the standardization of (semi)quantitative analysis and the application of VOI delineation methods (e.g. semi-automatic, manual, or CT-based) are essential. To ensure the successful implementation of quantitative nuclear imaging in new applications and indications, it is essential for researchers and clinicians to collaborate multidisciplinary in identifying appropriate methodologies. Establishing and sharing standardized approaches through publications and guidelines will be crucial in advancing the field and improving the comparability and reliability of future studies.

Other clinical quantitative PET applications

In PET imaging, quantification methods can be broadly categorized into semi-quantitative and absolute quantification. Semi-quantitative analysis involves comparing relative metabolic activity between regions of interest, often using SUVs, whereas absolute quantification measures the exact concentration of a radiotracer in a specific tissue. A commonly used example of semi-quantitative analysis in clinical practice is the Deauville scoring system for assessing treatment response in Hodgkin lymphoma and certain types of non-Hodgkin lymphoma [6]. This method involves visually comparing the [^{18}F]FDG uptake in residual tumor lesions to that in reference regions such as the mediastinum and liver on PET scans. The score is based on relative uptake rather than absolute quantitative values like the SUV, making it a practical and reproducible tool for clinicians to monitor treatment response.

In addition to the chapters in this thesis addressing two novel applications of (semi) quantitative PET, various other directions are currently discussed in the literature, holding significant potential for further exploration. For instance, (semi)quantitative evaluation may aid in differentiating between physiological and pathological uptake [8-12], distinguishing benign from malignant diseases [12-15], enhancing therapy response monitoring in oncology [16-20], and sarcoidosis [21, 22], and improving radiotherapy planning by refining target delineation [23]. Its utility extends beyond the current scope of this thesis, offering opportunities in diagnostics and treatment across various medical disciplines.

Reduction tracer administration in PET

Recent advancements in nuclear medicine, particularly in hardware (e.g. digital detectors), and software (post-processing and reconstruction algorithms, e.g. including those that use artificial intelligence (AI)), have created opportunities for optimizing tracer administration in clinical PET/CT imaging. These innovations ensure the necessity of finding a balance between high-quality imaging and minimizing radiation exposure. However, literature on tracer reduction strategies for new scanners is limited, necessitating further evaluation by each institution to identify and validate the options available for their specific scanners. **Chapter 4** describes the possibilities in tracer administration reduction per bed position at our institution, allowing for the selection of the protocol/dosing schedule to be adopted in clinical practice.

Frequent scanning may be necessary for recurrence detection and therapy response monitoring. In these situations, it is essential to minimize the radiation dose as much as possible. Furthermore, reducing tracer administration and/or scan time could enable new applications for (quantitative) PET. This includes achieving a low enough dose to facilitate imaging in pregnant women [24, 25], and in the pediatric population [26], as well as enabling faster imaging for intensive care patients [27]. In addition to the potential indications, [^{18}F]FDG-PET is used to non-invasively assess the metabolic activity of brown adipose tissue [28, 29], providing insight into its role in thermogenesis and energy expenditure, relevant for metabolic disorders like obesity and diabetes. This is typically done in healthy volunteers, where the level of radiation exposure deemed acceptable by a Medical Ethics Review Committee is limited, which makes the use of a lower administered activity particularly advantageous.

Efforts in recent years have focused on optimizing attenuation correction (AC) in nuclear medicine to reduce radiation exposure. AI reconstruction can be applied to convert a low-dose CT scan into improved image quality or by using ultra-low-dose CT with tin filters for AC [30]. Additionally, innovations that eliminate the need for CT, such as utilizing the low-level inherent radiation from PET crystals [31, 32], employing synthetic CT data [33], and

reconstructing AC images from the PET emission data using Maximum Likelihood Attenuation and Activity [34], are currently being investigated. These AC innovations, combined with the high sensitivity of modern scanners, allow for rapid imaging at doses low enough to support PET screening in high-risk populations (e.g. cancer, Alzheimer's disease) [35].

Clinical applications for quantitative SPECT

Quantitative SPECT is an emerging imaging technology, however, as with any new technology, its success depends on whether routine clinical applications can be identified. Key opportunities include the potential use of quantitative SPECT for response prediction in oncology (e.g. breast cancer, **chapter 6**), pre- and post-treatment dosimetry [36-38], improving personalized radiopharmaceutical therapy. Furthermore, in cardiac imaging, quantitative SPECT holds potential for perfusion analysis (**chapter 5**) and amyloidosis [39]. While there is a growing trend towards using PET over SPECT for MPI, SPECT remains a cost-effective and widely accessible option, as most healthcare facilities are equipped with SPECT rather than PET. This widespread availability, coupled with lower operational costs, makes SPECT a practical choice in many clinical settings, particularly in resource-limited environments.

As highlighted in the literature, quantitative SPECT is expected to play a significant role in several routine clinical applications, such as assessing liver remnant function [40-42] and diagnosing neurodegenerative disorders [43, 44]. It also enhances lesion assessment for osteoarthritis and arthroplasty using bone-seeking tracers [45, 46]. Moreover, (quantitative) SPECT can use dual-isotope imaging where two tracers are injected at the same time and acquired simultaneously by the SPECT system. This allows clinicians to assess multiple physiological processes, such as myocardial perfusion and imaging of cardiac sympathetic innervation, in a single scan, rather than requiring separate imaging sessions. This consolidation into one hospital visit minimizes patient discomfort and accelerates clinical decision-making, ultimately leading to faster initiation of appropriate treatment strategies [47].

Recent advancements, including the development of digital multi-detector cadmium-zinc-telluride (CZT) ring-shaped SPECT/CT systems, have eliminated the need for camera rotation, thereby improving both imaging speed and resolution. These innovations enable dynamic three-dimensional (3D) assessments, the generation of time-activity curves, and the quantification of coronary flows, similar to the capabilities traditionally associated with cardiac PET [48]. Moreover, the extraction of quantitative parameters in additional applications, such as dynamic 3D renography [49], has also become feasible. These advancements hold the potential to provide comprehensive quantitative SPECT imaging in settings where PET technology and the necessary infrastructure are not available.

FUTURE PERSPECTIVES

Standardization of quantitative PET and SPECT

There is substantial diversity in scanners and regional preferences globally, which complicates direct comparisons between studies. As a result, data often differ across institutions, making validation and implementation more challenging. Standardization and harmonization of quantification protocols are critical to ensure consistent and reproducible results across different institutions.

Quantitative parameters in PET and SPECT are significantly influenced by various technical factors, such as differences in equipment, acquisition protocols, reconstruction settings, and processing software. These variations make it challenging to establish standardized threshold values for discriminating between true and false positives or distinguishing between healthy and diseased states. In response to this challenge, the European Association of Nuclear Medicine (EANM) launched the EANM Research Ltd. (EARL) initiative (also used in **chapter 4**), aiming to harmonize quantification in nuclear medicine imaging. Currently, EARL primarily focuses on oncology PET studies. To support the standardization of both PET and SPECT, EARL has already published guidelines for acquisition protocols, interpretation, and reporting of quantitative imaging. Future accreditation programs, such as those offered by EARL, may play a crucial role in further standardizing quantitative PET and SPECT across different medical centers, thereby enhancing the reliability of future research and facilitating multicenter studies.

Long-axis field-of-view PET: Advancements in Imaging Technology

Long-axis field-of-view (LAFOV) PET scanners allow whole-body imaging with high sensitivity, providing high resolution temporal and spatial information across multiple organ systems simultaneously. The LAFOV PET provides advantages such as reduced radiation exposure, enhanced image quality, shorter acquisition times, and the ability to effectively image tracers with low radioactivity.

Earlier in this chapter, the possibilities for reducing tracer administration in PET with standard oncology tracers, such as [^{18}F]FDG, for sensitive scanners were discussed, and this also applies to the “ultra-sensitive” LAFOV PET/CT. However, for tracers like [^{89}Zr]-labelled monoclonal antibodies used in immunoPET, short-axis FOV (SAFOV) systems face challenges due to the long half-life (78.4 h) and non-usable emissions, limiting injected activity for radiation dosimetry. LAFOV systems overcome these limitations with higher sensitivity, enabling faster acquisitions, reducing motion risks, and enhancing tumor-to-background contrast [50]. This is particularly beneficial for [^{89}Zr]-labelled tracers targeting immune-related biomarkers (e.g. VEGF, PD-L1, HER2, or CD8 expression), as it aids in predicting responses to immunomodulatory treatments.

As described in **chapter 2,** imaging with [^{82}Rb]Cl, which has a short half-life of 75 s, is suitable for clinical cardiac perfusion imaging. However, acquiring late-phase images of the Na+/K+ ATPase function using [^{82}Rb]Cl, suggested as a potential biomarker for prostate and breast cancer, is challenging with SAFOV scanners [50]. The high sensitivity and timing resolution of LAFOV PET systems are expected to tackle this issue and enhance imaging of short half-life tracers as [^{82}Rb]Cl. This advancement may broaden its clinical indications, including potential use in renal perfusion imaging.

Conventional PET offers dynamic imaging over a limited FOV, while LAFOV PET enables dynamic assessment across larger areas. A key benefit is the ability to perform dynamic scanning of individual body regions, including visualization of the major vessels, which enables consistent extraction of an IDIF, thereby eliminating the need for arterial blood sampling. Nevertheless, venous sampling remains necessary for metabolite analysis. For drug development, the use of such a LAFOV scanner is particularly advantageous.

The high sensitivity and timing resolution of LAFOV scanners enable the acquisition of dynamic data, allowing for the extraction of high-quality lesion and arterial blood time-activity curves [51, 52]. These curves can be used to calculate parameters with potentially greater biological significance and specificity than commonly used static measures like the SUV [53]. This capability could significantly enhance the clinical evaluation of systemic diseases. However, challenges remain including the high costs and resource demands due to long scan times and substantial computational power required to process large datasets. Expanding dynamic PET datasets and multicenter studies are crucial for advancing quantitative imaging, for example in developing prediction tools that support clinical decision-making.

Respiratory motion significantly hinders the PET evaluation of lesions in the lower thorax. The high sensitivity of the LAFOV PET scanners, however, facilitates the application of breath-holding during shorter acquisition periods. Cui et al. (2024) showed that a 30-second acquisition and breath-hold make PET/CT both clinically feasible and more accurate [54]. This methodology effectively reduces background lung uptake and significantly improves both lesion registration and quantification, particularly in the lower thoracic region. Such advancements highlight the potential of this approach in overcoming challenges associated with respiratory motion during PET imaging.

Conclusion

Technologically, extensive capabilities are already in place, yet the broader clinical implementation of quantitative PET and SPECT is limited by the slow process of gathering sufficient evidence to support their use in new clinical applications. This slow accumulation of robust clinical data hinders the widespread adoption of quantitative PET and SPECT, limiting the number of patients who can benefit from their potential advantages.

While quantitative PET and SPECT have proven effective in established areas, future research is critical to validate their expanded applications. Overcoming the evidence gap will enable these technologies to guide more tailored treatment strategies and improve clinical outcomes for a broader range of diseases. This thesis makes a modest contribution by exploring several novel applications of quantitative PET and SPECT, highlighting their potential for broader implementation, but there is still a long way to go. By continuing to advance research in this field, these powerful diagnostic tools can be further optimized, ensuring that more patients benefit from their capabilities.

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