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**Advancing Quantitative Imaging in Long Axial Field-of-View
PET/CT: Clinically Feasible Parametric Imaging, Ground-
Truth-Validated Motion Correction and Assessment of
System Robustness**

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List of Abbreviations

abbreviation	definition
3D	three-dimensional
4D	four-dimensional
AUC	area under the curve
C_0	plasma compartment
C_1	reversible tissue compartment
C_2	metabolically trapped compartment
CT	computed tomography
CV	coefficient of variation
dB	decibel
DDB	defective detector block
DEA	detector electronics assembly
DV	distribution volume
EARL2	EANM Research Ltd version 2 (EARL2)-compliant reconstruction protocol
EARL2-HS	EARL2-compliant reconstruction in high-sensitivity mode
EARL2-UHS	EARL2-compliant reconstruction in ultra-high-sensitivity mode
FALCON	Fast Algorithm for Motion Correction
[^{18}F]	fluorine-18
FDG / [^{18}F]FDG	fluorodeoxyglucose / fluorine-18-fluorodeoxyglucose
HighRes	high-resolution reconstruction protocol
HighRes-HS	HighRes reconstruction in high-sensitivity mode
HighRes-UHS	HighRes reconstruction in ultra-high-sensitivity mode
HS	high sensitivity
IDIF	image-derived input function
K_1	influx rate constant from plasma to tissue
k_2	efflux rate constant from tissue back to plasma
k_3	intracellular phosphorylation rate constant
k_4	dephosphorylation rate constant
kBq/mL	kilobecquerel per millilitre
K_i	net influx rate constant
LAFOV	long axial field of view
LORs	lines of response
LSO	lutetium oxyorthosilicate
LUAD	lung adenocarcinoma
LUSC	lung squamous cell carcinoma
MBq	megabecquerel
MC	Monte Carlo

MIP	maximum-intensity projection
MoCo	motion correction
MTV	metabolic tumour volume
NEMA	National Electrical Manufacturers Association
ns	non-significant
NSCLC	non-small cell lung cancer
OAR	organ at risk
OP-OSEM	ordinary Poisson ordered-subsets expectation maximisation
PBIF	population-based input function
PD-L1	programmed death-ligand 1
PET	positron emission tomography
p.i.	post-injection
PSMA / [¹⁸ F]PSMA-1007	prostate-specific membrane antigen / fluorine-18-labelled PSMA-1007
PSNR	peak signal-to-noise ratio
RD	relative difference
RNG	random number generator
ROI	region of interest
SAFOV	short axial field of view
SiFAlin-TATE / [¹⁸ F]SiFAlin-TATE	silicon-fluoride acceptor–modified tyrosine ³ -octreotate / fluorine-18-labelled SiFAlin-TATE
sPBIF	scaled population-based input function
SSIM	structural similarity index measure
SUV	standardised uptake value
t*	Patlak start time / equilibration time
TBR	tumour-to-background ratio
TPS	tumour proportion score
UHS	ultra-high sensitivity
V _b	fractional blood-volume contribution
VOI	volume of interest
XCAT	extended cardiac-torso

1 Introduction

Positron emission tomography (PET) is a molecular imaging technique that enables non-invasive assessment of physiological and metabolic processes in vivo. In contrast to primarily anatomical imaging modalities, such as computed tomography (CT), PET visualises the biodistribution of radiolabelled molecules by detecting pairs of 511 keV photons produced by positron–electron annihilation.

Historically, clinical PET was performed using short axial field-of-view (SAFOV) systems, typically covering 15–35 cm in the axial direction [1–3]. Because this limited axial coverage cannot encompass the entire clinically relevant body region in a single bed position, whole-body examinations using SAFOV PET systems require either multi-bed-position step-and-shoot imaging or continuous bed motion technology [4]. The restricted axial acceptance also limits system sensitivity. In SAFOV PET systems, less than 5% of emitted annihilation photons are detected [5]. Consequently, image quality and quantitative precision have historically been constrained by limited count statistics, particularly when acquisitions are shortened, injected activity is reduced, or dynamic data are divided into multiple temporal frames [6,7].

The introduction of long axial field-of-view (LAFOV) PET/CT systems has substantially changed this technical landscape [8–11]. By extending the axial field of view to one metre or more, LAFOV systems, such as the Biograph Vision Quadra (Siemens Healthineers, Knoxville, TN, USA), increase system sensitivity, with reported gains of up to 40-fold compared with conventional SAFOV scanners [5]. This increased sensitivity, combined with simultaneous coverage of large parts of the body, provides new opportunities for quantitative molecular imaging. In particular, LAFOV PET can acquire tracer kinetics across multiple organs and lesions within a single bed position, enabling total-body dynamic imaging. At the same time, the improved count statistics can support shorter acquisitions while preserving diagnostic image quality [12,13].

However, these technical advantages do not automatically translate into clinical utility for quantitative imaging. Higher sensitivity and extended axial coverage should be integrated into acquisition, correction, reconstruction, and quality-control strategies that are feasible in routine clinical workflows under realistic conditions. In this context, image enhancement is regarded as an interconnected process: radiopharmaceutical kinetics can be quantified by clinically feasible parametric imaging, spatial fidelity should be preserved by validated motion correction, and quantitative reliability should be maintained even when system performance is compromised by detector defects.

A first requirement for this translational pathway is the development of clinically feasible quantitative imaging beyond the standardised uptake value (SUV). SUV remains the most widely used PET metric because it is simple to calculate and can be derived from static clinical acquisitions. Nevertheless, SUV is a semi-quantitative measure that represents the time-averaged tissue activity concentration during a defined acquisition interval. It is commonly normalised by injected activity and body weight [14]. It is affected by uptake time, plasma glucose concentration, body composition, scanner calibration, and reconstruction settings. More importantly, in PET using fluorine-18-fluorodeoxyglucose ($[^{18}\text{F}]\text{FDG}$) PET, a radiolabelled glucose analogue that serves as a surrogate marker of glucose metabolism, SUV reflects a composite signal comprising tracer delivery, cellular transport, phosphorylation, tissue retention, blood-pool contribution, and washout. Consequently, SUV cannot distinguish whether increased uptake is driven by perfusion, irreversible trapping, or non-specific background activity [15,16].

Dynamic PET and kinetic modelling provide a more specific framework for quantification. By measuring tracer activity as a function of time and relating tissue activity curves to an input function, parametric imaging can estimate physiologically interpretable parameters at the voxel or lesion level. For $[^{18}\text{F}]\text{FDG}$, Patlak analysis and compartmental modelling are commonly used to estimate the net influx rate (K_i), which reflects irreversible tracer trapping, and the distribution volume (DV), which provides

information about the reversible component and vascular contribution [17,18]. These parameters can provide biological information complementary to SUV and may improve tumour-to-background contrast, lesion characterisation, and therapy-response assessment [19,20].

In non-small cell lung cancer (NSCLC), where histological subtype and programmed death-ligand 1 (PD-L1) status influence therapeutic decision-making, separating irreversible metabolic trapping from delivery- or blood-volume-related components may provide clinically relevant information [21–23]. Since PD-L1 expression has been associated with altered glucose metabolism and increased [^{18}F]FDG uptake in NSCLC [24,25], additional kinetic parameters that separate irreversible [^{18}F]FDG trapping from delivery- or distribution-related effects may provide additional information about PD-L1-related tumour biology.

Despite this potential, [^{18}F]FDG parametric imaging has not yet entered routine clinical practice. Conventional [^{18}F]FDG dynamic protocols often require prolonged acquisitions of up to 60 min, starting at the time of tracer injection. Such protocols are difficult to integrate into high-throughput clinical schedules and may cause discomfort for patients [26,27]. Abbreviated [^{18}F]FDG dynamic scan protocols have been developed for SAFOV PET systems, with the aim of shortening dynamic acquisition duration [28,29]. However, dynamic reconstruction divides the available data into multiple short temporal frames, which increases image noise when count statistics are limited. LAFOV PET directly addresses part of this limitation by providing higher sensitivity across a larger axial field of view range, but protocol optimisation remains essential. The relevant clinical question is not only whether parametric imaging can be performed, but also whether it can be performed within an acquisition window that is acceptable for routine practice while preserving quantitative agreement with longer reference protocols.

The first objective of this thesis was to optimise abbreviated dynamic [^{18}F]FDG PET protocols for parametric imaging on an LAFOV PET/CT system. The work focused on

optimising dynamic and Patlak reconstruction protocols, including framing configurations and examination duration. The aim was to reduce the dynamic acquisition from 60 min to a 10–20 min examination window while preserving K_i and DV estimates relative to patient-specific reference approaches. The resulting protocol was then applied to a larger cohort of treatment-naïve NSCLC patients to investigate whether parametric metrics could provide additional information for histological subtype characterisation and PD-L1 assessment.

A second requirement for reliable quantitative LAFOV PET is spatial fidelity. Extended axial coverage enables simultaneous total-body or multi-organ imaging, and improved sensitivity reduces statistical noise. Despite the performance enhancements provided by LAFOV PET, patient motion remains unavoidable and residual motion-induced blurring prevents these systems from realising their full performance potential. This issue is particularly relevant for dynamic and parametric imaging, where motion between temporal frames can distort time-activity curves and propagate errors into kinetic parameter estimates. Although the high sensitivity of LAFOV PET enables short static acquisitions that reduce the likelihood of gross body motion [30], respiratory motion remains unavoidable during thoracic and abdominal imaging.

Respiratory and body motion can degrade quantitative imaging in different ways. Lesion motion during PET acquisition causes spatial blurring, reduced apparent uptake, impaired lesion localisation, and biased lesion volume estimates. In lung nodules, motion-related errors of up to 30% in SUV and up to 21% in PET-derived tumour volume have been reported [31]. These effects are important in the thorax and upper abdomen, where respiration can lead to underestimation of SUV_{mean} and SUV_{max} and overestimation of metabolic tumour volume (MTV) [32–34]. Because treatment-response assessment and lesion characterisation rely on changes in quantitative metrics, uncorrected motion may affect both diagnostic interpretation and quantitative comparability.

Motion-correction techniques have become an important component of advanced PET

imaging, including data-driven and image-based approaches developed for respiratory and whole-body motion management [35–37]. A limitation of clinical evaluations is the absence of a true motion-free reference in patient data. Living subjects cannot provide an experimentally controlled, motion-free condition. Clinical evaluations often rely on visual scoring or semi-quantitative metrics. These approaches are insufficient to determine whether a correction algorithm recovers the underlying tracer distribution or merely changes image appearance. The second objective of this thesis was to establish and use a Monte Carlo simulation framework tailored to the Biograph Vision Quadra, combined with a digital four-dimensional extended cardiac-torso (XCAT) phantom [38], to generate patient-like LAFOV PET data with controlled respiratory motion and a corresponding motion-free reference [39]. This framework was used to quantify respiratory motion artefacts and to validate motion-correction strategies in terms of lesion uptake, morphology, volume, image noise, and agreement with the reference condition.

Although motion-correction methods can improve quantitative accuracy by reducing motion-induced bias, their clinical utility also depends on the stability and reliability of the imaging system on which they are implemented. Therefore, a third requirement for clinical translation is system robustness. Quantitative PET assumes that scanner performance remains stable and that quality-control procedures identify hardware conditions that could compromise image quality or quantification. Detector blocks are routinely evaluated during quality control and may be classified as defective when parameters such as energy resolution, photopeak position, or count-rate behaviour fall outside predefined thresholds [40–43]. If the number or configuration of defective blocks exceeds vendor-defined limits, scanner operation may be interrupted for recalibration, maintenance, or hardware replacement. Such interruptions can reduce patient throughput and increase operational burden.

Previous investigations of defective detector blocks (DDBs) have focused mainly on SAFOV PET systems. These studies suggest that small numbers of isolated DDBs may

have limited quantitative impact, whereas clustered defects can degrade image quality and diagnostic confidence [44,45]. LAFOV PET systems differ substantially from SAFOV scanners because they contain more detector elements and have considerably higher sensitivity. For example, the Biograph Vision Quadra comprises 1,216 detector blocks and 243,200 crystals, compared with 304 detector blocks and 60,800 crystals in a conventional Biograph Vision 600 system [8,46]. These differences suggest that LAFOV systems may tolerate selected sparse detector defects better than SAFOV systems. Nevertheless, the tolerance limits for LAFOV PET are not established, particularly with respect to the number of DDBs and their spatial distribution.

The third objective of this thesis was to investigate the robustness of LAFOV PET/CT to DDBs and to determine how the number of defects, their spatial distribution, and reconstruction settings influence quantitative accuracy. Defects were simulated in patient and phantom datasets to evaluate clinically relevant metrics such as SUV_{mean} , SUV_{max} , and image noise. This approach was designed to assess whether current quality-control assumptions are overly conservative for LAFOV PET.

Taken together, LAFOV PET provides the physical basis for improved quantitative imaging, but clinical utility depends on the ability to convert this physical advantage into clinically feasible and quantitatively accurate imaging. Parametric imaging with an abbreviated [^{18}F]FDG scan protocol addresses clinical feasibility and radiopharmaceutical kinetics; motion correction and its validation address spatial accuracy and the reliability of quantitative recovery; and detector-defect assessment addresses operational robustness and confidence in scanner performance. The central hypothesis of this thesis is that the technical advantages of LAFOV PET can be translated into clinically meaningful quantitative image enhancement when these three requirements are considered together.

2 Technical and Methodological Background

This chapter summarises the scanner, kinetic, motion-correction, quality-control, and simulation concepts used in the following studies.

2.1 LAFOV PET/CT Systems and the Biograph Vision Quadra as a Quantitative Imaging Platform

PET scanner design has evolved through improvements in detector material, timing resolution [47], reconstruction methodology [48], and scanner geometry [49]. One of the most important recent hardware developments is the extension of the axial field of view. LAFOV PET systems provide axial coverage of more than one metre [50]. This extended axial field of view allows simultaneous imaging of a large fraction of the patient and therefore transforms PET from a primarily sequential whole-body acquisition technique into a platform for simultaneous multi-organ imaging.

The main physical consequence of the extended axial field of view is increased system sensitivity. Greater axial detector coverage subtends a larger solid angle around the patient, so a higher fraction of annihilation photon pairs contributes to measured coincidence events. This increase in sensitivity improves event statistics.

Several LAFOV and total-body PET/CT systems have been introduced, including the uEXPLORER (United Imaging, Shanghai, China) with 194 cm axial coverage, the PennPET Explorer (University of Pennsylvania, Philadelphia, PA, USA) with 142 cm axial coverage, and the Biograph Vision Quadra with 106 cm axial coverage [8–10].

The studies in this thesis were performed using the Biograph Vision Quadra. Its technical characteristics are therefore important for interpreting the subsequent methodological studies. The Biograph Vision Quadra combines 106-cm axial coverage with silicon photomultiplier-based detector technology, time-of-flight capability and a detector architecture comprising 1,216 detector blocks. It provides a radial spatial resolution of 3.27 mm (full width at half maximum, at a 1-cm axial position) [8].

The detector system of the Biograph Vision Quadra PET scanner has a four-level hierarchical architecture comprising individual lutetium oxyorthosilicate (LSO) crystals, detector mini blocks, detector blocks, and detector electronics assemblies (DEAs). The basic detection element is an LSO crystal measuring $3.2 \text{ mm} \times 3.2 \text{ mm} \times 20 \text{ mm}$ and coupled to a silicon photomultiplier. 25 LSO crystals are arranged in a 5×5 array to form a detector mini block. 8 mini blocks are arranged in a 2×4 matrix to form a detector block, and 16 detector blocks are arranged in an 8×2 matrix to form a DEA. The complete scanner contains 76 DEAs arranged in 4 axial rows, each comprising 19 assemblies distributed around the transaxial circumference. Of note, a single DEA is the smallest physical unit that could be replaced during maintenance. The hierarchical detector architecture and the scanner-level configuration are illustrated in **Figure 1**.

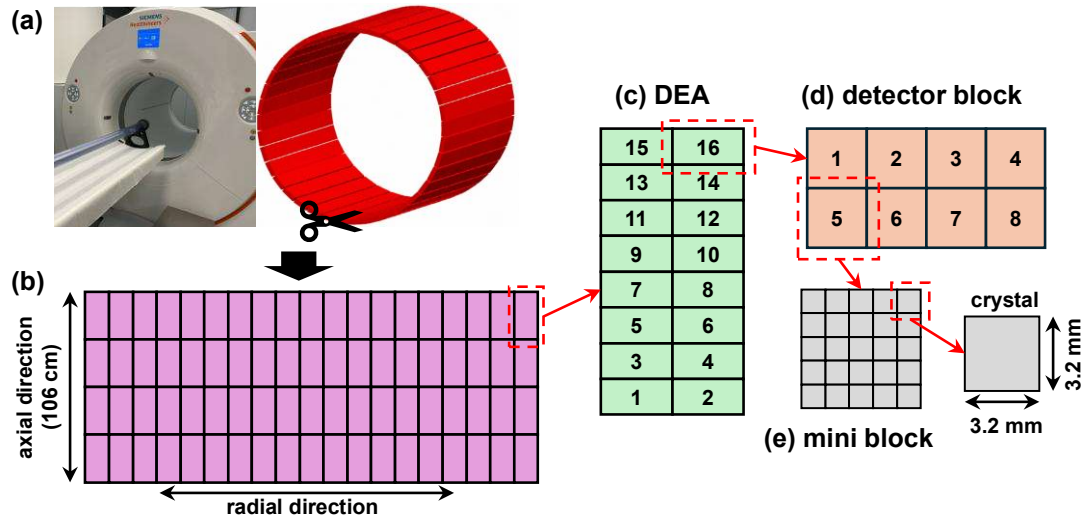


Figure 1 Hierarchical architecture of the Biograph Vision Quadra PET detector system. (a) Photograph of the Biograph Vision Quadra PET scanner and schematic representation of its cylindrical detector ring. (b) Unrolled layout of the detector ring, showing 4 axial rows, each containing 19 detector electronics assemblies (DEAs) distributed around the transaxial circumference, for a total of 76 DEAs and an axial extent of 106 cm. Each purple box identifies a single DEA. (c) Configuration of a DEA, consisting of 16 detector blocks arranged in an 8×2 matrix. (d) Configuration of a detector block, consisting of 8 detector mini blocks arranged in a 2×4 matrix. (e) Configuration of a detector mini block, consisting of a 5×5 array of lutetium oxyorthosilicate (LSO) crystals. Each crystal measures $3.2 \text{ mm} \times 3.2 \text{ mm} \times 20 \text{ mm}$. The red dashed boxes and arrows indicate the successive enlargement of the detector components, from a DEA to an individual crystal.

A distinctive feature of the Biograph Vision Quadra is the availability of two sensitivity modes that differ in the axial range of accepted lines of response (LORs). In high-sensitivity (HS) mode, the maximum axial acceptance angle is 18° , whereas in ultra-high-sensitivity (UHS) mode it is 52° . The HS and UHS modes and their corresponding sensitivity profiles are illustrated in **Figure 2**.

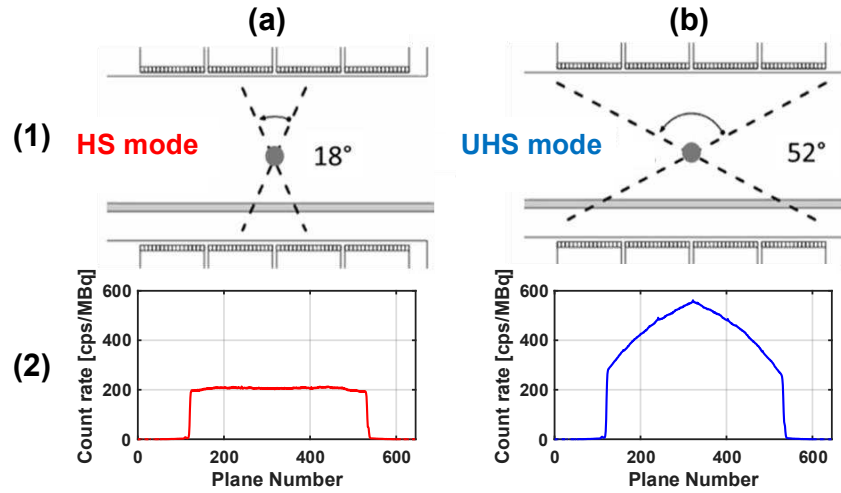


Figure 2 Sensitivity modes and axial sensitivity profiles of the Biograph Vision Quadra long axial field-of-view PET/CT system. (1) Schematic geometry of (a) high sensitivity (HS) mode with an axial acceptance angle of 18° and (b) ultra-high sensitivity (UHS) mode with an axial acceptance angle of 52° . (2) Axial sensitivity profiles measured according to the National Electrical Manufacturers Association (NEMA) NU 2-2018 standard.

The wider angular acceptance in UHS mode increases the nominal system sensitivity from 83 kcps/MBq to 176 kcps/MBq [8]. This increase is accompanied by a different axial sensitivity profile and greater reliance on correction and reconstruction models for highly oblique LORs [51,52]. The distinction between HS and UHS modes functions not only as a technical setting but also as a recurring methodological variable in this thesis. It affects image-derived input functions and Patlak reconstructions in parametric imaging with an abbreviated [^{18}F]FDG scan protocol. It is also considered when evaluating the ability of LAFOV PET to tolerate detector block defects.

2.2 Tracer Kinetic Modelling and [^{18}F]FDG Parametric Imaging

Static imaging cannot distinguish the underlying kinetic and non-specific signal contributions to lesion uptake. Tracer kinetic modelling addresses this limitation by describing the temporal exchange of a radiotracer between plasma and tissue compartments. The number and interpretation of kinetic parameters depend on the tracer and the biological process being modelled.

The most widely used oncological PET tracer, [^{18}F]FDG is a glucose analogue. It is suitable for imaging glucose metabolism. [^{18}F]FDG transport from plasma into tissue is described by the influx rate constant K_1 , and its return from tissue to plasma is described by the efflux rate constant k_2 . Intracellular phosphorylation is described by the rate constant k_3 , and dephosphorylation from the phosphorylated compartment back to the free tissue compartment is represented by k_4 [53,54].

For lesion analysis, [^{18}F]FDG kinetics are commonly modelled with an irreversible two-tissue compartment model [55]. Under this approximation, exchange out of the phosphorylated compartment is assumed to be negligible over the clinically relevant imaging interval, such that dephosphorylation is neglected and k_4 is set to zero [17]. This assumption forms the basis of clinical Patlak analysis, in which irreversible tracer trapping is estimated from dynamic PET data after equilibration of the reversible compartments. A schematic representation of the irreversible two-tissue compartment model is shown in **Figure 3**.

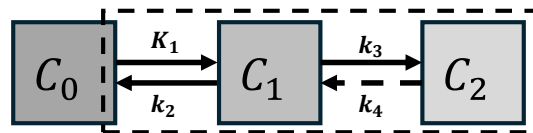


Figure 3 Irreversible two-tissue compartment model for [^{18}F]FDG kinetics. The plasma compartment (C_0) delivers unmetabolised [^{18}F]FDG to the reversible tissue compartment (C_1) through the influx rate constant K_1 , and efflux from C_1 to C_0 is described by k_2 . Intracellular phosphorylation from C_1 to the metabolically trapped compartment (C_2) is described by k_3 . In the irreversible approximation used for clinical Patlak analysis, dephosphorylation from C_2 to C_1 is assumed to be negligible during the imaging interval and k_4 is fixed at 0.

Under this irreversible approximation, the net influx rate constant K_i summarises irreversible [^{18}F]FDG trapping and is related to the microparameters by:

$$K_i = \frac{K_1 \cdot k_3}{k_2 + k_3} \quad (1)$$

In this context, K_i provides a physiologically interpretable measure of net [^{18}F]FDG accumulation, whereas the Patlak intercept, denoted as the distribution volume in this thesis, represents the apparent contribution of reversible tissue and vascular activity to the measured signal. For an ideal irreversible two-tissue compartment model without explicit blood-volume correction, the reversible component of the Patlak intercept is related to K_1 and k_2 as follows:

$$DV \approx \frac{K_1 \cdot k_2}{(k_2 + k_3)^2} + V_b \quad (2)$$

where V_b denotes the fractional blood-volume contribution. Equations (1) and (2) illustrate why K_i and DV provide complementary information. K_i reflects irreversible metabolic trapping, whereas DV reflects tracer delivery, reversible distribution, and vascular contribution.

Patlak graphical analysis provides a practical linearisation for tracers with irreversible trapping after a suitable equilibration time t^* . For each voxel or volume of interest, the tissue time-activity curve $C_t(t)$ is combined with the arterial plasma input function $C_p(t)$. The Patlak equation can be written as:

$$\frac{C_t(t_n)}{C_p(t_n)} = K_i \cdot \frac{\int_0^{t_n} C_p(\tau) d\tau}{C_p(t_n)} + DV \quad t_n > t^* \quad (3)$$

The equilibration time, t^* , is the time point at which the reversible compartments of the tracer reach a steady state, after which the graphical plot becomes linear. The slope of the linear relationship is K_i , and the intercept is DV [17]. A schematic diagram of graphical Patlak analysis is shown in **Figure 4**.

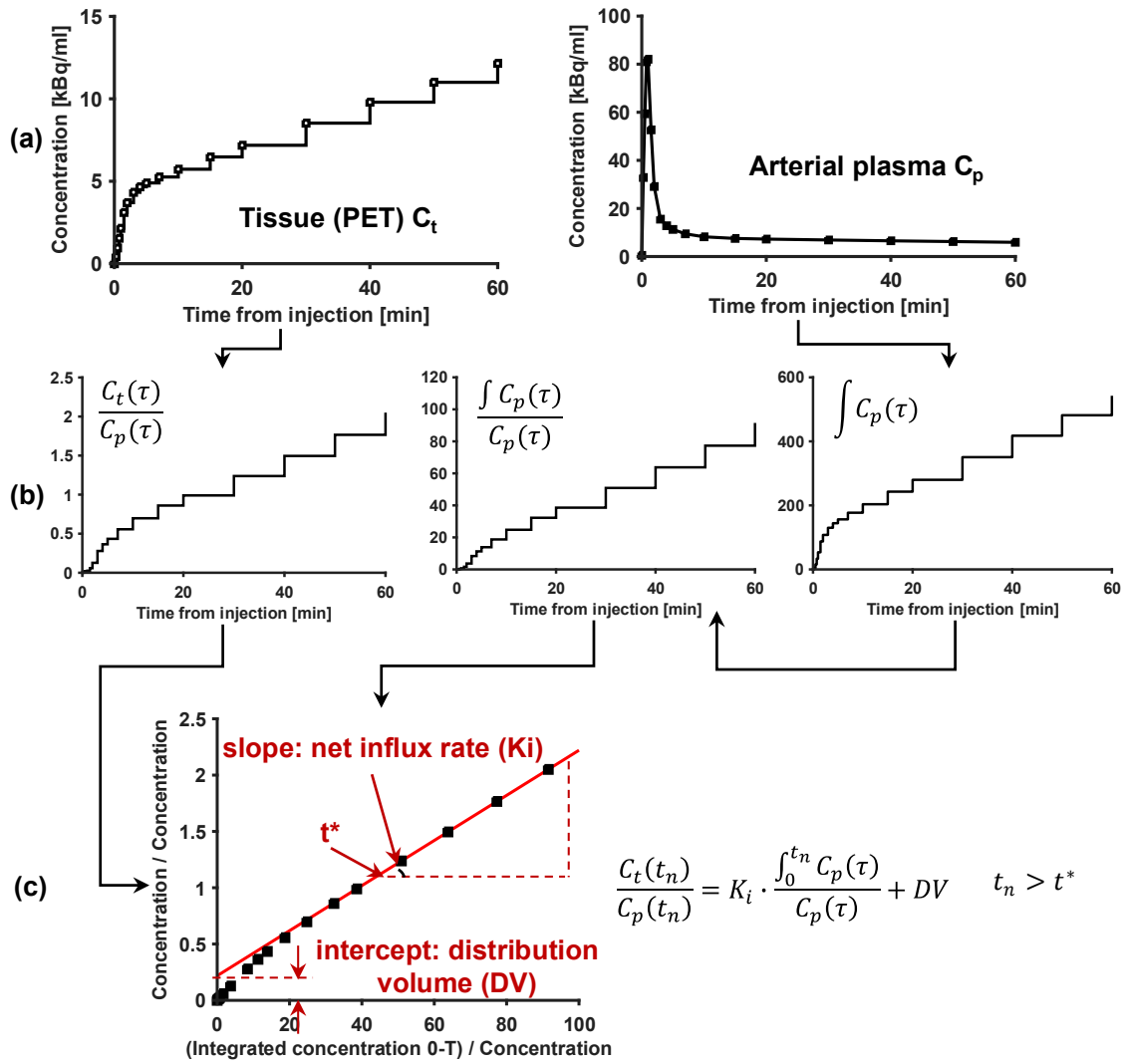


Figure 4 Schematic Patlak graphical analysis for irreversible tracer uptake. (a) Tissue time-activity curve $C_t(t)$ and arterial plasma input function $C_p(t)$ after tracer injection. The concentration curves are schematic. (b) Derived Patlak variables, including the tissue-to-plasma concentration ratio $C_t(t)/C_p(t)$ and the time-integrated plasma input function normalised by plasma concentration, $\int C_p(\tau)/C_p(\tau)$. (c) Patlak plot after equilibration of reversible compartments. The slope of the linear phase equals the net influx rate constant K_i , and the y-intercept equals the distribution volume DV .

In conventional graphical Patlak analysis (indirect Patlak), dynamic PET data are first reconstructed into a series of temporal image frames, and the Patlak regression is then applied voxel-wise to the reconstructed frames. This post-reconstruction approach is straightforward and broadly applicable. However, the spatially varying and correlated noise in those frames is difficult to model and can propagate into the resulting parametric

maps, because voxel-wise fitting is performed on independently reconstructed dynamic frames [56,57].

Direct Patlak reconstruction, also referred to as four-dimensional parametric reconstruction, incorporates the Patlak model directly into the iterative reconstruction process [18,58]. Instead of estimating kinetic parameters after frame-by-frame image reconstruction, the kinetic parameters are estimated from the dynamic emission data while accounting for the Poisson statistics of the measurements. This approach can reduce frame-noise propagation and improve parametric image quality, particularly when the available temporal frames are short or the acquisition is abbreviated [58,59]. Direct Patlak reconstruction is central to the first part of this thesis, where abbreviated LAFOV [^{18}F]FDG protocols are optimised.

Accurate kinetic modelling requires an arterial input function, defined as the time course of radiotracer concentration in arterial plasma. Continuous arterial sampling is regarded as the reference standard, but it is invasive and difficult to incorporate into routine clinical workflows [26,60]. Non-invasive alternatives include the image-derived input function (IDIF), which is extracted from dynamic PET images by delineating a large blood pool such as the aorta or left ventricle, and the population-based input function (PBIF), which represents an average arterial curve derived from a population and individualised by scaling to late venous samples or late image-derived blood-pool values [61–64]. When a PBIF is scaled to the individual patient, it is referred to as a scaled population-based input function (sPBIF).

The feasibility of abbreviated [^{18}F]FDG parametric imaging depends on the input-function strategy. For full dynamic imaging, an IDIF can be obtained from data acquired from the time of tracer injection onward, including the early bolus peak. In an abbreviated late acquisition, the early bolus is not measured in the individual patient. For [^{18}F]FDG K_i estimation, this limitation is partly mitigated because Patlak slope estimation is driven primarily by the integrated input function and the late linear phase rather than by the exact

peak amplitude alone [62]. This provides the rationale for PBIF-based protocols, in which a population input function supplies the early portion of the curve and individual late measurements provide patient-specific scaling [63–65]. This principle is tracer- and model-dependent and should not be generalised to all radiotracers without validation.

LAFOV PET improves the practical conditions for parametric imaging in two ways. First, the extended field of view allows simultaneous measurement of blood-pool activity and target tissue kinetics across a large anatomical range. In SAFOV PET, an IDIF can be derived from the heart or aorta, but truly simultaneous and continuous sampling of both the input function and distant lesions is constrained by the limited axial coverage. Second, the higher sensitivity of LAFOV PET improves the count statistics of short dynamic frames. Together with direct Patlak reconstruction and individualised input-function strategies, these properties support the development of clinically feasible parametric [^{18}F]FDG protocols.

2.3 Motion in LAFOV PET and Motion Correction Strategies

Motion is a major source of bias in quantitative PET. It arises from respiration, cardiac contraction, swallowing, bowel motion and voluntary or involuntary body movement. For lesions in thoracoabdominal regions, respiratory motion can reduce apparent SUV, broaden the spatial extent of uptake, impair lesion localisation and overestimate MTV [31,33,34]. These effects remain relevant in LAFOV PET. LAFOV PET acquisitions frequently include thoracic and abdominal regions within the same bed position, where respiratory displacement is most pronounced. High sensitivity and reduced image noise can make residual motion artefacts more visible, because the limiting factor becomes spatial fidelity rather than coincidence event statistics alone [37]. Motion correction becomes an essential component of quantitative LAFOV PET, especially when uptake, lesion volume and parametric estimates are used for clinical quantification [30].

Motion-management methods can be categorised according to how motion information is obtained and how the acquired data are used. Traditional approaches rely on external

or sensor-based surrogates, such as respiratory belts, pressure sensors, optical tracking systems or marker-based systems [66–69]. These approaches provide a motion signal independent of the PET data and can be useful for respiratory gating. However, they require additional hardware, increase setup complexity and may not accurately represent internal organ motion. Furthermore, gating alone discards or down-weights part of the acquired dataset and therefore increases image noise unless the discarded events are compensated by longer acquisition time [70].

Sensor-free approaches are particularly attractive for LAFOV PET because they can exploit the high event statistics of the PET acquisition itself. The advantage of this strategy is its compatibility with routine clinical acquisition, because no external surrogate is required. Its limitation is that the motion signal and correction quality depend on tracer distribution, count statistics, lesion location and the robustness of the signal-extraction algorithm [70,71].

Data-driven methods are a type of sensor-free approach. Data-driven methods estimate respiratory or body-motion signals from listmode data or sinograms [72–74]. In respiratory applications, the extracted signal can be used to define gates, estimate deformation fields and combine information into a motion-corrected image [36,37]. A representative approach used in this thesis is the vendor-specific data-driven method OncoFreeze AI (Siemens Healthineers, Knoxville, TN, USA), implemented on the Biograph Vision Quadra. This method derives respiratory information from PET listmode data, uses automated anatomical parsing to identify relevant anatomical regions, and applies elastic motion correction based on motion deblurring [36,75,76]. The workflow of this data-driven method is shown in **Figure 5**.

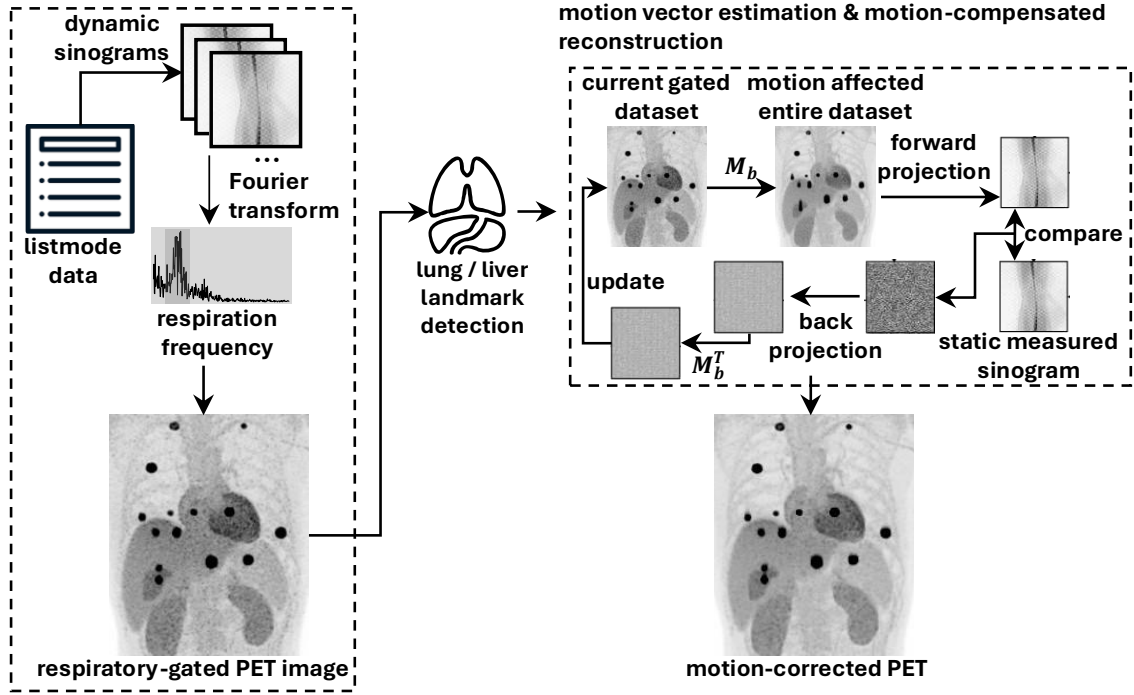


Figure 5 Workflow of OncoFreeze AI data-driven respiratory motion correction for PET. PET listmode data are transformed into dynamic sinograms and used to estimate respiratory frequency and reconstruct respiratory-gated PET images. Automated anatomical landmark detection identifies the lung and liver regions, after which motion vectors are estimated and applied during motion-compensated reconstruction to generate the motion-corrected PET image.

Image-based motion correction estimates motion from reconstructed image series. The data are divided into short temporal frames or gates; each frame is reconstructed, and registration is used to transform the frames into a common reference position before recombination. Different algorithms for image-based motion correction have been developed [77–79]. The Fast Algorithm for Motion Correction (FALCON; Medical University of Vienna, Austria) is one representative image-based approach for fast motion correction of dynamic total-body PET studies [35]. Such methods are relatively vendor-independent and can be applied to dynamic data, but their performance depends on the quality of the short-frame images and on the accuracy of image registration [35,80].

Deep-learning methods have also been proposed for automatic motion estimation and inter-frame correction, particularly in dynamic PET applications [81]. These methods can

model complex spatial and temporal patterns [82,83], but their generalisability depends on training data, tracer distribution and validation strategies [84].

2.4 System Robustness and Quality Control

Reliable quantitative imaging requires stable scanner performance. PET detector blocks comprise scintillation crystals, photodetectors and associated electronics that determine energy estimation, timing, crystal identification and count-rate performance. Routine PET/CT quality control monitors detector performance and identifies detector blocks that fail predefined criteria, for example because of abnormal photopeak position, degraded energy resolution or abnormal count rates [40–43]. A block that does not meet performance criteria may be classified as a DDB.

During reconstruction, coincidence events involving a DDB can be excluded or masked, and the resulting sinogram defects may be corrected by sinogram-repair or normalisation-related correction procedures to reduce visible artefacts and quantitative bias [44,45,85,86]. However, the loss of detector blocks removes the corresponding LORs and changes the angular and axial sampling of the acquisition [45,87,88]. The quantitative impact depends not only on the number of affected blocks, but also on their spatial distribution [44]. Sparse defects may have limited impact because neighbouring detector elements and the high overall sensitivity partly compensate for missing LORs. Clustered defects can create localised sensitivity losses and spatially structured artefacts that are more difficult to compensate [45].

Of note, the Biograph Vision Quadra scanner should be taken out of service if quality-control testing identifies 10 or more malfunctioning detector mini blocks. Once this threshold is reached or exceeded, the scanner should undergo recalibration and, if necessary, replacement of the affected components.

Therefore, system robustness is a methodological component of quantitative PET. If quality-control thresholds are too conservative, scanners may be withdrawn from clinical

service despite preserved quantitative performance. If thresholds are too permissive, localised biases may affect lesion uptake, image noise or response-assessment metrics.

2.5 Monte Carlo Simulation, Digital Twins and Digital Phantoms for Validation

Monte Carlo (MC) simulation is a computational method based on repeated random sampling of probabilistic physical processes. In PET, MC simulation can model positron emission, annihilation photon transport, attenuation, scatter, detector interactions, coincidence processing and data acquisition. Geant4 and the OpenGATE ecosystem are widely used frameworks for these purposes in medical physics [89–91]. MC simulation is particularly useful when experimental conditions must be controlled precisely or when the desired datasets cannot be obtained directly in a clinical study.

For this thesis, the relevant concept is not general MC simulation alone, but a validated digital twin of the Biograph Vision Quadra. A digital twin is an *in silico* model that reproduces essential components of a physical scanner and its data pathway. The Biograph Vision Quadra digital twin used in this research models scanner geometry, detector materials, detector response, coincidence generation and listmode output, and it has been validated against physical measurements [39]. Because the simulated data can be processed with the same reconstruction infrastructure used for measured data, including vendor-specific investigational prototype software, time-of-flight information, point-spread-function modelling and defined sensitivity modes, this framework enables controlled comparisons that remain close to the clinical reconstruction workflow.

This digital-twin framework is central to this thesis. In the motion-correction study, it was combined with a digital anthropomorphic phantom to generate both motion-free and motion-affected acquisitions with known respiratory displacement. By simulating the same tracer distribution with and without motion, the framework enables motion-correction methods to be evaluated not only in terms of visual improvement but also by their agreement with a known motion-free reference.

In the detector-defect analysis, patient data provided clinically realistic but heterogeneous conditions, which limited the ability to isolate the effects of the defects. The Biograph Vision Quadra digital twin enables controlled variation of activity levels and phantom configurations for the assessment while keeping all other factors constant.

3 Materials and Methods

3.1 Integrated Study Design and Common PET/CT Platform

All clinical and simulation-based studies were centred on the Biograph Vision Quadra PET/CT system. Unless stated otherwise, PET images were reconstructed using the investigational prototype software e7 tools (Siemens Healthineers, Knoxville, TN, USA) with ordinary-Poisson ordered-subsets expectation maximisation (OP-OSEM), using 4 iterations, 5 subsets, point-spread-function modelling, and time-of-flight information enabled. High-resolution reconstructions (HighRes) were generated with a $440 \times 440 \times 645$ matrix and an isotropic voxel size of 1.65 mm without post-reconstruction filtering. For analyses requiring harmonised and smoothed reconstructions, an additional EARL2-compliant reconstruction was performed using a $220 \times 220 \times 645$ matrix, $3.30 \times 3.30 \times 1.65$ mm³ voxels, and a 4-mm Gaussian post-filter. Reconstructions were performed in HS and UHS modes when required to evaluate the influence of axial acceptance angle and count statistics on quantitative performance.

Relative differences (RDs) were used throughout the quantitative analyses to compare modified datasets with their respective reference datasets. For image-noise analyses, the coefficient of variation (CV) was estimated from a 30-mm-diameter spherical VOI placed in homogeneous liver tissue in patient or patient-like phantom datasets, as appropriate. CV was defined as

$$CV = \frac{C_{std}}{C_{mean}} \times 100\% \quad (4)$$

where C_{mean} and C_{std} denote the mean and standard deviation of the activity concentration within the VOI, respectively.

Unless otherwise specified, continuous data were reported as means and standard deviations, and two-sided p-values below 0.05 were considered statistically significant.

3.2 Clinical Feasibility of Abbreviated Dynamic [^{18}F]FDG Parametric Imaging

3.2.1 Dynamic Acquisition Cohort and Input-function Extraction

Dynamic [^{18}F]FDG PET data were analysed from 6 oncological patients (4 females, 2 males; age, 60 ± 20 years; body weight, 76.1 ± 28.2 kg). PET emission data were acquired continuously for 65 min on the Biograph Vision Quadra system. [^{18}F]FDG was administered intravenously approximately 15 s after the start of PET acquisition (injected activity, 240.6 ± 82.8 MBq). The listmode data were acquired with all available LORs and subsequently reconstructed in HS and UHS modes. A low-dose CT scan was acquired for attenuation correction and anatomical localisation. The study was approved by the local institutional review board (KEK 2019-02193), and all patients provided written informed consent in accordance with the Declaration of Helsinki.

A total of 26 lesions were delineated by an experienced nuclear medicine physician using an iso-contour tool in PMOD 4.1 (PMOD Technologies, Zurich, Switzerland) with a threshold set to 50% of SUV_{max} .

Patient-specific IDIFs were extracted from the descending thoracic aorta using an investigational automated VOI tool (SnakeVOI; Siemens Healthineers, Knoxville, TN, USA). The tool performed CT-based aortic landmarking and generated a snake-shaped VOI within the descending aorta [92]. The resulting mean VOI volume across the 6 patients was 2.13 ± 0.51 cm³. These VOIs were transferred to the dynamic PET frames to extract the mean aortic activity concentration over time. Automatic aortic localisation was successful in all patients without manual correction [59].

The 65-min dynamic data were framed as 2×10 s, 30×2 s, 4×10 s, 8×30 s, 4×60 s, 5×120 s, and 9×300 s using the HighRes protocol. The area under the curve (AUC) was determined for each patient-specific IDIF, and the RD between HS and UHS reconstructions was used to quantify sensitivity-mode bias and precision.

3.2.2 Direct Patlak Reconstruction with IDIF

Ki and DV images were reconstructed directly from the dynamic emission data. The direct Patlak reconstruction used a nested expectation-maximisation algorithm [93] with 8 iterations, 5 subsets, point-spread-function and time-of-flight modelling, followed by a 2-mm Gaussian filter [94]. Lesion Ki and DV values were extracted from the lesion VOIs delineated on SUV images. The initial direct Patlak evaluation used patient-specific IDIFs as input functions. Parametric images generated by a 4×300 s direct Patlak reconstruction with the IDIF served as the reference for the corresponding sensitivity mode.

To investigate the influence of the number of Patlak frames on the estimation of parametric values, data from 45 min (t^*) to 65 min post-injection were reconstructed using 5×240 s and 6×200 s frames, which were used as Patlak frames for parametric image reconstruction. Ki and DV were determined for both sensitivity modes. Their biases and precisions were reported relative to the reference values obtained for the respective sensitivity mode.

3.2.3 Scaled Population-based Input Functions and Abbreviated Scan

Configurations

To generate patient-specific sPBIFs, the normalised PBIF from Sari et al. [63] was scaled by the ratio of the patient-specific partial-IDIF AUC to the normalised-PBIF AUC, with both AUCs calculated from t^* to the end of the scan, as described by the following formula:

$$sPBIF_{0 \rightarrow t_{end}} = PBIF_{0 \rightarrow t_{end}} \times \left(\frac{AUC_{IDIF}(t \rightarrow t_{end})}{AUC_{PBIF}(t \rightarrow t_{end})} \right) \quad (5)$$

where $AUC_{IDIF}(t \rightarrow t_{end})$ and $AUC_{PBIF}(t \rightarrow t_{end})$ denote the AUCs of the patient-specific partial IDIF and the normalised PBIF, respectively, from t to the end of the scan t_{end} . $sPBIF_{0 \rightarrow t_{end}}$ and $PBIF_{0 \rightarrow t_{end}}$ denote the scaled PBIF and normalised PBIF from tracer injection to the end of the scan.

The AUC of the final 10-min segment (55–65 min post-injection, p.i.) of each patient-specific partial IDIF was used to scale the normalised PBIF, as determined by Sari et al. [63], to obtain a patient-specific sPBIF. The workflow for scaling the normalised PBIF to a patient-specific sPBIF is shown in **Figure 6**.

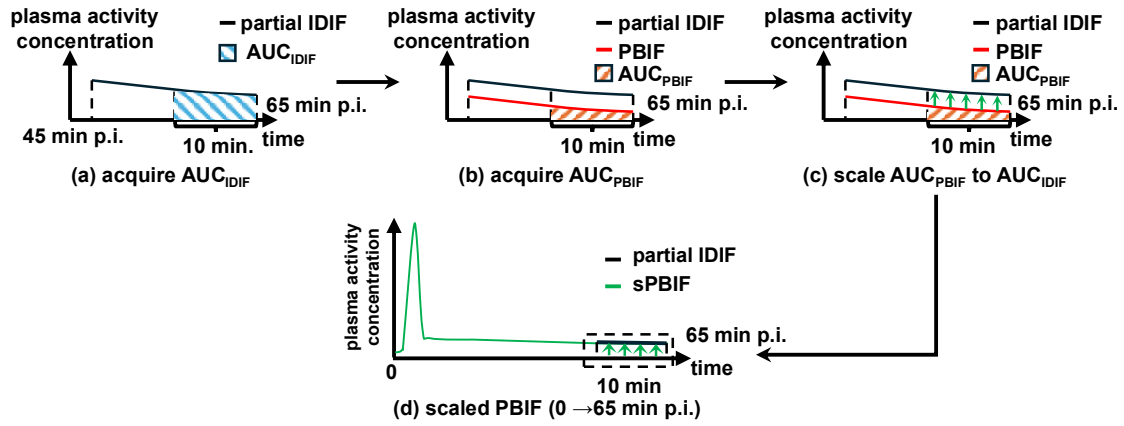


Figure 6 Generation of a patient-specific scaled population-based input function (sPBIF) for abbreviated [^{18}F]FDG Patlak imaging. (a) Area under the curve (AUC) of the patient-specific partial image-derived input function (IDIF) from 55 to 65 min post-injection (partial AUC_{IDIF}). (b) The AUC of the normalised population-based input function (AUC_{PBIF}) over the same interval. (c) Scaling of AUC_{PBIF} to match partial AUC_{IDIF} . (d) Resulting patient-specific sPBIF from tracer injection to 65 min post-injection (p.i.). Curves are schematic.

To explore clinically feasible acquisition configurations, including scan duration and the number of Patlak frames, patient-specific sPBIFs were used for direct Patlak reconstruction. The IDIF-based reconstruction using the same sensitivity mode and number of Patlak frames served as the reference. The main protocol window was 45–65 min p.i. with $t^* = 45$ min. Data from additional abbreviated windows of 50–65 and 55–65 min p.i. were reconstructed to determine whether the acquisition could be shortened below 20 min while preserving quantitative accuracy.

To evaluate the impact of the number of Patlak frames on sPBIF-based direct Patlak estimates for abbreviated scan durations, the final 20, 15, and 10 min of the scans were used, as listed in **Table 1** [59].

Table 1 Dynamic scan windows and Patlak frame schemes for abbreviated direct Patlak reconstruction. The table lists the Patlak start time (t^*) and temporal framing used for 4-, 5-, and 6-frame reconstructions for scan windows of 45–65, 50–65, and 55–65 min post-injection (p.i.) [59].

scan window	t^* [min]	4-frame scheme	5-frame scheme	6-frame scheme
45–65 min p.i.	45 min	4×300 s	5×240 s	6×200 s
50–65 min p.i.	50 min	4×225 s	5×180 s	6×150 s
55–65 min p.i.	55 min	4×150 s	5×120 s	6×100 s

Parametric Ki and DV images obtained with sPBIF-based direct Patlak reconstruction were compared with the corresponding patient-specific IDIF reference images. SUV images reconstructed from the 60–65 min p.i. interval were included as the conventional clinical comparator. Image-level agreement was assessed using signed and absolute RD, the structural similarity index measure (SSIM), and peak signal-to-noise ratio (PSNR). Tumour-to-background ratio (TBR) was calculated as the lesion peak value divided by the mean value in a 3-cm spherical liver VOI. PSNR was defined as:

$$PSNR = 10 \times \log \left(\frac{(peakval)^2}{MSE} \right) \quad (6)$$

where *peakval* denotes the maximum value within the image intensity range and *MSE* denotes the mean squared error between the estimated and reference images.

Linear regression was used to assess agreement between HS and UHS estimates. For direct Patlak comparisons, paired Student's t-tests were used to compare Ki and DV bias at each Patlak start time, and two-way analysis of variance was used to assess the effects of sensitivity mode and the number of Patlak frames on Ki and DV bias. Analyses were performed using SPSS Statistics 29.0 (IBM, Armonk, NY, USA) and MATLAB (version: R2023b; MathWorks, Natick, MA, USA).

3.3 Clinical Translation of Abbreviated [^{18}F]FDG Parametric Imaging to NSCLC

After the abbreviated 45–65 min protocol for [^{18}F]FDG PET/CT had been optimised, it was applied to a larger clinical cohort to determine whether the additional kinetic

information from Ki and DV could support the characterisation of NSCLC tumour subtype and PD-L1 status.

3.3.1 Patient Cohort and PET/CT Acquisition

Patients were selected from a prospective PET/CT registry between July 2023 and January 2025. 91 patients with suspected NSCLC underwent abbreviated dynamic [^{18}F]FDG PET/CT. Patients were excluded if histopathological confirmation was unavailable, if the lesions were benign or inflammatory, or if histology confirmed metastasis from another known malignancy. The patient selection workflow is shown in **Figure 7**.

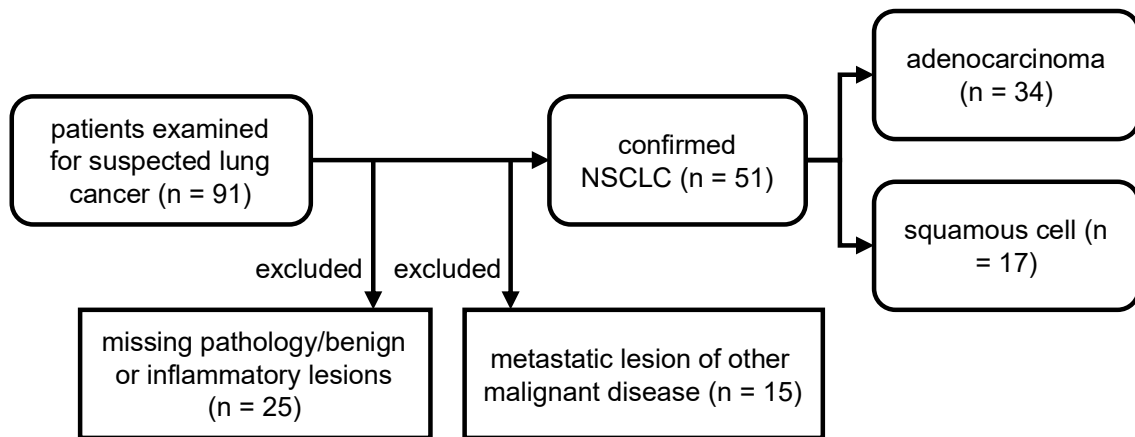


Figure 7 Patient-selection flow diagram for the non-small cell lung cancer (NSCLC) cohort. Of 91 patients examined for suspected lung cancer, 51 had histologically confirmed NSCLC and were included; 25 were excluded because histopathological confirmation was unavailable or lesions were benign/inflammatory, and 15 were excluded because lesions represented metastases from other malignancies. Included patients were classified as lung adenocarcinoma (n = 34) or lung squamous cell carcinoma (n = 17). n = number of patients.

The final cohort consisted of 51 treatment-naïve patients with histopathologically confirmed NSCLC, including 34 patients with lung adenocarcinoma (LUAD) and 17 with lung squamous cell carcinoma (LUSC). The study was approved by the institutional review board of the University Hospital of Tübingen (383/2025BO2), and all patients provided written informed consent.

Patients fasted for at least 10 h, and blood glucose levels were required to be less than

200 mg/dL before tracer administration. [^{18}F]FDG was administered intravenously at 3.0 MBq/kg. A 20-min PET acquisition was performed from 45 to 65 min p.i. with patients in the supine position, covering the region from the vertex to the mid-thigh. If no contraindications were present, diagnostic contrast-enhanced CT was acquired before PET for attenuation correction and morphological correlation.

3.3.2 SUV and Direct Patlak Image Reconstruction

SUV images were reconstructed in both HS and UHS modes using the protocol described in **section 3.1**. Parametric Ki and DV images were reconstructed using the optimised abbreviated direct Patlak workflow. The 20-min acquisition was divided into four 5-min Patlak frames. Direct Patlak reconstruction was performed in both HS and UHS modes using the direct Patlak protocol described in **section 3.2**. Partial IDIFs (45–65 min p.i.) were extracted from the descending aorta using automated CT-based segmentation (SnakeVOI). The AUC from the final 10 min of the acquisition (55–65 min p.i.) was used to scale a population-based input function as described previously [63], yielding a patient-specific sPBIF from 0 to 65 min p.i. for direct Patlak reconstruction. Representative SUV and parametric images from one patient are shown in **Figure 8**.

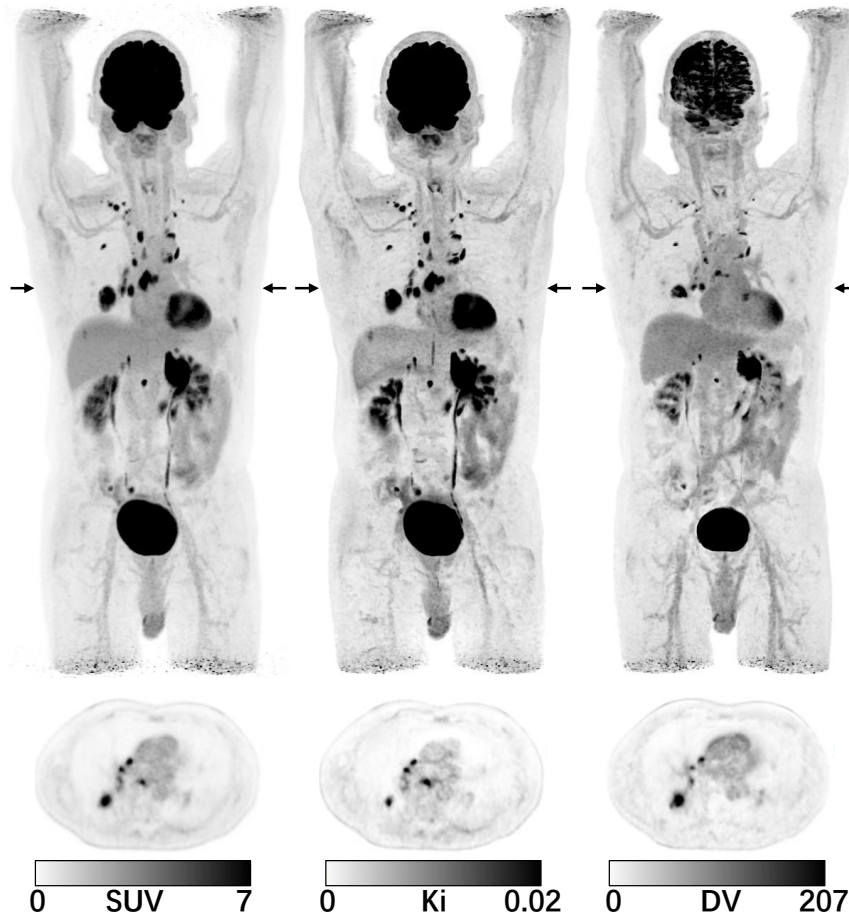


Figure 8 Representative SUV, Ki, and DV images in a patient with histologically confirmed lung adenocarcinoma. Maximum-intensity projections are shown above corresponding axial slices at the arrow-marked lesion locations. Ki = net influx rate constant in units of (mL/cm³/min); DV = distribution volume in the units of (%).

3.3.3 Lesion Quantification and Statistics

Suspicious malignant lesions were delineated independently for each image using a 41% iso-contour threshold. Lesions were required to have an MTV of at least 1 mL and corresponding morphological findings on CT. The axial position of each delineated lesion was measured. RDs in SUV, Ki, and DV between HS and UHS modes were calculated.

Only UHS-based images were used for PD-L1 status and lesion subtype analysis. Histological subtype and PD-L1 tumour proportion score (TPS) were obtained from tissue sampling. PD-L1 positivity was defined as $TPS \geq 1\%$. Statistical analyses were

performed using GraphPad Prism 9.4.1 (GraphPad Software). Normality was assessed using the D'Agostino–Pearson test. Continuous variables were compared using the Mann–Whitney U test. Correlations between lesion axial position and the RDs in quantitative metrics between HS and UHS modes were examined using either the Pearson correlation coefficient or Spearman's rank correlation coefficient, with Bonferroni correction applied to the resulting p-values.

3.4 Quantification of Respiratory Motion Correction with Motion-Free Ground Truth

3.4.1 Patient Cohorts and PET Reconstruction

Two patient cohorts were analysed, each including 10 patients. The first cohort underwent fluorine-18-labelled silicon-fluoride acceptor–modified tyrosine³-octreotate ([¹⁸F]SiFAlin-TATE) PET/CT for somatostatin receptor imaging of neuroendocrine tumours (age, 61 ± 8 years; body weight, 89 ± 18 kg; injected activity, 191 ± 35 MBq). The second cohort comprised patients with lung cancer who underwent [¹⁸F]FDG PET/CT (age, 70 ± 8 years; body weight, 78 ± 11 kg; injected activity, 156 ± 21 MBq). PET data were acquired for 5 min at 90 min p.i. ([¹⁸F]SiFAlin-TATE) or 60 min p.i. ([¹⁸F]FDG). PET images were reconstructed using the HighRes protocol in UHS mode (HighRes-UHS). The study was approved by the institutional review board (773/2021BO2), and written informed consent was obtained from all patients.

3.4.2 Patient-like XCAT Phantom and Monte Carlo Simulation

Motion-free ground truth was unavailable in clinical datasets. To replicate patient respiratory motion patterns and generate the motion-free ground truth, a 50th-percentile adult female XCAT phantom [38] (height: 163 cm; weight: 66 kg) was implemented and combined with controlled respiratory motion patterns. A 5-min [¹⁸F]FDG acquisition corresponding to an injected activity of 2 MBq/kg was simulated. 14 spherical lesions with diameters of 10 and 15 mm were placed in the lung and abdominal regions and

assigned activity concentrations of 7, 14, and 28 kBq/mL to represent a range of lesion contrasts, as shown in **Figure 9(a)**.

Two respiratory motion patterns derived from clinical patient examinations were implemented with maximum amplitudes of 2 and 3 cm. Simulations were performed using the Biograph Vision Quadra digital twin described in **section 2.5** [39], and the simulated listmode data were reconstructed with the same protocol as the patient data. To validate the implemented motion model, the respiratory signal was re-extracted from the simulated PET data using the data-driven method. The close agreement between the prescribed and re-extracted waveforms confirmed accurate reproduction of the intended respiratory motion (**Figure 9(b)**). For each simulated acquisition with respiratory motion, a corresponding motion-free dataset was generated and served as the motion-free reference for objective quantification of the residual error remaining after respiratory motion correction (**Figure 9(c)**).

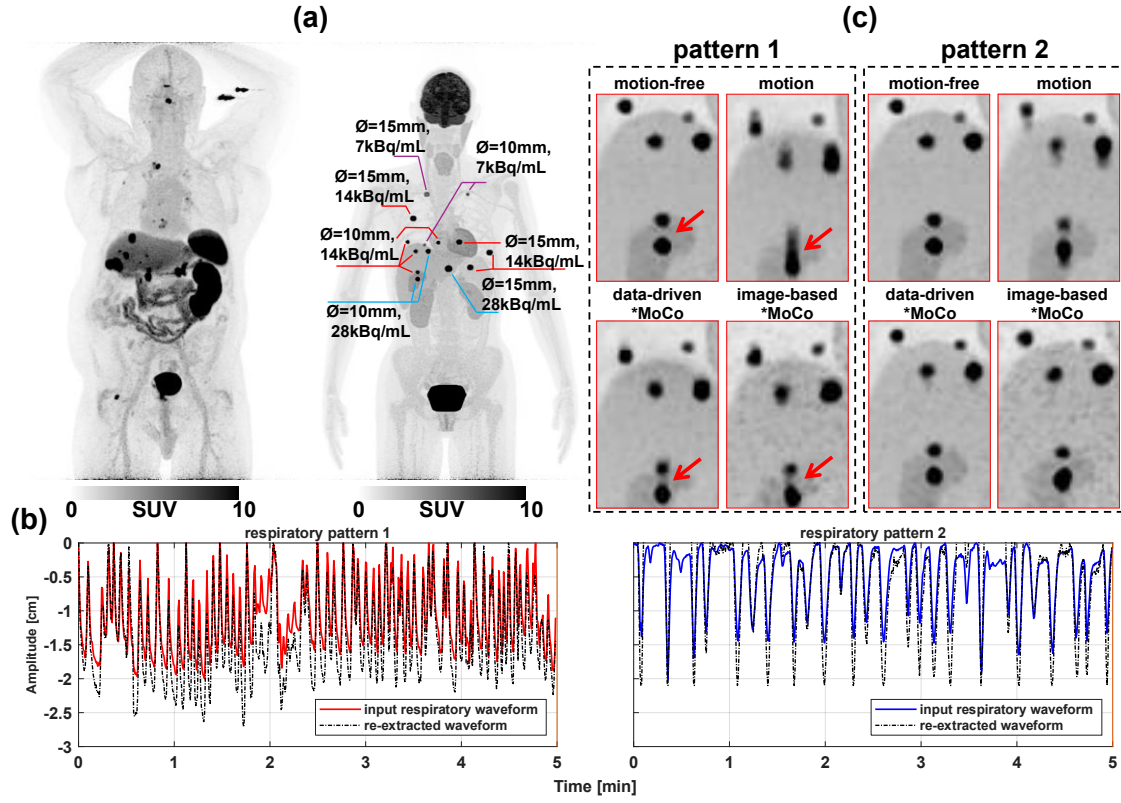


Figure 9 Patient-like digital-twin framework for objective benchmarking of respiratory motion correction (MoCo). (a) Clinical PET maximum-intensity projection (left) and corresponding extended cardiac-torso digital phantom (right), with simulated liver and lung lesions labelled by diameter ($\varnothing$, mm) and activity concentration (kBq/mL). (b) Patient-derived respiratory waveforms over a 5-min acquisition for respiratory patterns 1 and 2; solid lines show prescribed simulation input, and dashed lines show respiratory signals re-extracted from simulated PET data. (c) Representative simulated PET images for both respiratory patterns showing the motion-free reference, respiratory motion, data-driven motion correction with OncoFreeze AI, and image-based motion correction with FALCON. FALCON = Fast Algorithm for Motion Correction.

3.4.3 Motion-correction Workflows

Two distinct motion-correction strategies, a data-driven method and an image-based method, were evaluated. The data-driven method was OncoFreeze AI [36,76]. The image-based method was FALCON (Medical University of Vienna) [35].

Because the selected image-based method was originally designed for dynamic PET series rather than static acquisitions, a dedicated processing workflow was established. The original listmode data were rebinned into 150 consecutive 2-s frames. A single frame was selected to serve as the reference frame. The image-based multiscale registration

algorithm, FALCON, was then applied to align the remaining 149 frames to this reference. The co-registered images were then averaged to generate the final motion-corrected image. This workflow is illustrated in **Figure 10**.

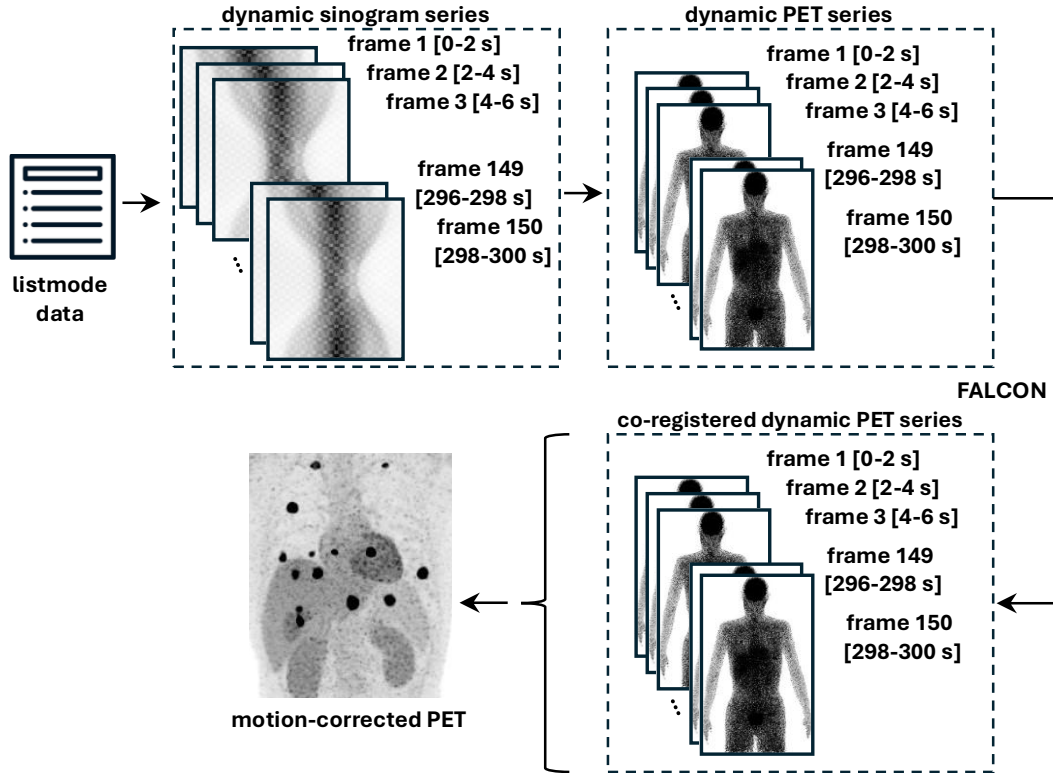


Figure 10 Image-based FALCON motion-correction workflow. PET listmode data from a 300-s acquisition were rebinned into 150 consecutive 2-s frames and reconstructed as a dynamic PET series. FALCON co-registered the dynamic frames to a reference frame, and the co-registered images were averaged to generate a 300-s motion-corrected static PET image. FALCON = Fast Algorithm for Motion Correction.

3.4.4 Lesion Quantification and Statistics

Tumour nodules in the clinical cohorts and simulated lesions in the patient-like phantom were segmented using 3D Slicer (Version 5.8.2) [95] and Hermes Affinity (Version 5.0.1; Hermes Medical Solutions, Stockholm, Sweden) with a 50% threshold of SUV_{max} . Segmentation was performed independently for all uncorrected, corresponding motion-corrected, and motion-free reference datasets.

For the clinical datasets, respiratory motion correction was evaluated using the RD relative to the corresponding uncorrected images. To avoid over-representing patients

with multiple lesions, lesion measurements were first averaged at the patient level within each anatomical region before statistical analysis.

For phantom lesion analyses, lesion-level means were used. Correction-induced RDs, calculated relative to the corresponding uncorrected images, were compared between correction methods and between the patient and phantom datasets. In the phantom datasets, recovery relative to the motion-free reference was assessed using signed relative error, allowing identification of under- or overestimation after correction.

To assess the impact of motion correction on image noise, CV was estimated from both patient and patient-like phantom datasets.

Normality was assessed with the Shapiro–Wilk test. Paired t-tests or Wilcoxon signed-rank tests were used for paired method comparisons. Respiratory pattern and amplitude effects were assessed using lesion-level paired contrasts of signed relative error. Pattern effects were evaluated after averaging over amplitudes, and amplitude effects were evaluated after averaging over respiratory patterns. Analyses were performed using MATLAB (version: R2026a; MathWorks).

3.5 Quantitative Robustness to Defective Detector Blocks

3.5.1 Patient Data and Phantom Simulations

10 oncological patients were included in the DDB analysis (3 females, 7 males; age, 71 ± 11 years; body weight, 82.0 ± 14.1 kg). 7 patients underwent clinically indicated fluorine-18-labelled prostate-specific membrane antigen-1007 (^{18}F]PSMA-1007) PET/CT and 3 underwent ^{18}F]FDG PET/CT. Mean injected activity was 179.0 ± 28.3 MBq for ^{18}F]PSMA-1007 and 149.7 ± 25.8 MBq for ^{18}F]FDG; corresponding uptake times were 90 ± 3 min and 59 ± 4 min. A 5-min PET acquisition was performed after diagnostic contrast-enhanced CT. At the time of acquisition, the PET/CT system was fully operational, and no detector blocks were defective. The study was conducted with institutional review board approval (730/2022BO2) and in accordance with the

Declaration of Helsinki.

As no physical phantom of comparable size was readily available, for controlled spatial analysis, a large cylindrical digital phantom with a diameter of 40 cm and a length of 106 cm was simulated for 5 min at [^{18}F] activity concentrations of 0.25, 0.5, 1.0, and 2.0 kBq/mL. The phantom was centred within the axial and transaxial field of view. Simulations were based on the Biograph Vision Quadra digital twin described in **section 2.5** [39].

The DDB simulation workflow with the Biograph Vision Quadra digital twin was further validated against measurements using a physical cylindrical phantom (diameter, 5.5 cm; length, 140 cm) filled with an aqueous [^{18}F] solution of 2.2 kBq/mL. The same geometry and activity distribution were replicated in simulation (**Supplementary Figure 3** [96]).

3.5.2 Simulation of Defective Detector Blocks and Reconstruction

Hardware-level deactivation of individual detector blocks was not performed on the clinical scanner. Instead, DDBs were simulated after acquisition by selectively removing coincidence events associated with predefined detector blocks from the listmode data using a vendor-specific tool. The listmode datasets with removed events were binned into sinograms and reconstructed into images. Normalisation-based compensation for the missing detector contributions was applied during reconstruction. The original datasets without simulated defects served as references, allowing direct quantification of defect-induced deviations. An overview of the described workflow is shown in **Figure 11** [96].

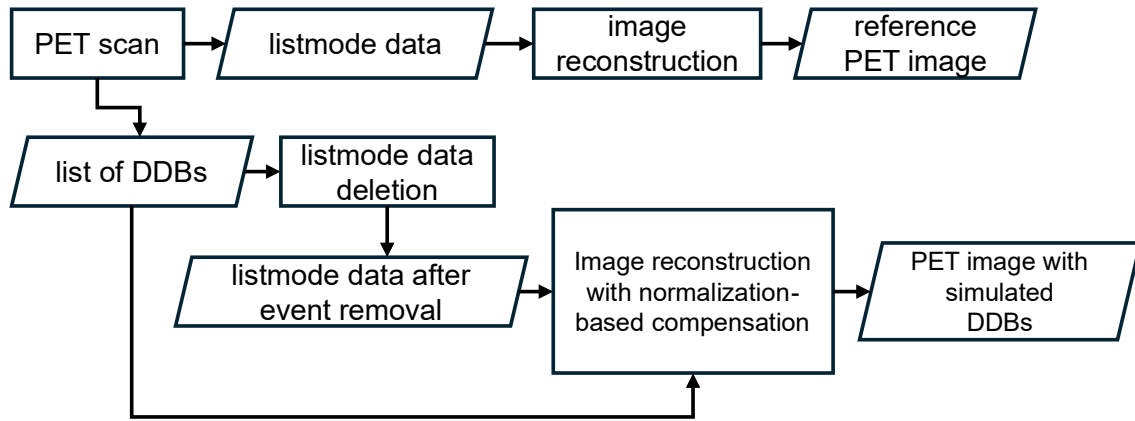


Figure 11 Processing workflow for reference and defective-detector-block-affected datasets. Original listmode data were reconstructed as reference images without detector defects. For defective detector block (DDB) simulations, events associated with predefined detector blocks were removed from the listmode data before sinogram binning and image reconstruction with normalisation-based compensation. Reference and DDB-affected images were processed in parallel for quantitative comparison [96].

Two defect categories were evaluated: sparse and clustered defects comprising adjacent detector blocks. For patient data, sparse DDB scenarios included 1, 2, 4, 8, 16, 32, 64, and 128 DDBs. Five random-number generator seeds were used for each sparse scenario to sample different spatial distributions. Clustered defects were modelled as the loss of 4, 8, and 16 adjacent blocks. Each defect size was assessed at 12 positions, defined by the combination of four axial locations and three angular positions. Of note, the 16 adjacent blocks corresponded to one complete DEA.

For phantom simulations, single-block defects, linear arrangements, partial and full-DEA clustered defects, and sparse configurations of 1, 4, 8, and 16 blocks were evaluated. Representative patterns of these defect scenarios are shown in **Figure 12** [96].

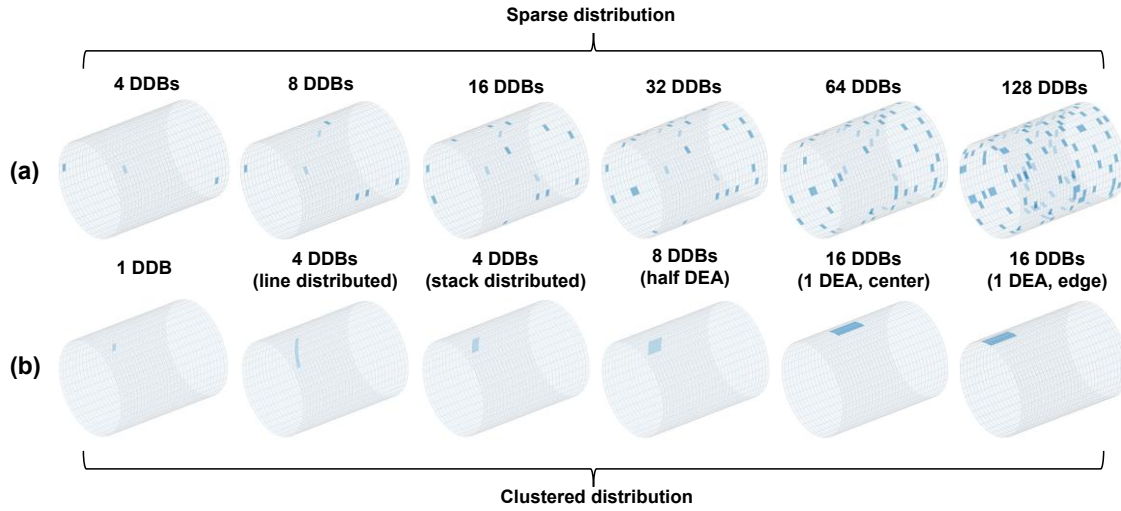


Figure 12 Schematic representations of selected simulated DDB patterns across the PET system. (a) Sparse DDB distributions ranging from 4 to 128 blocks. (b) Clustered DDB distributions ranging from 1 to 16 blocks, including configurations up to a full detector electronics assembly (DEA) [96].

All reference and DDB-affected data were reconstructed using HighRes and EARL2-compliant reconstructions in both HS and UHS modes.

3.5.3 Patient and Phantom Quantification

For the patient-based analysis, 30 lesions were delineated on the reference PET images without simulated DDBs using a 50% threshold of SUV_{max} (mean lesion volume, 1.0 ± 2.0 mL). Lesion VOIs were then applied to the corresponding DDB-affected images. SUV_{mean} and SUV_{max} were extracted from each lesion. Image noise was quantified using the CV. The RD between each DDB-affected dataset and the corresponding reference dataset was calculated for SUV_{mean} , SUV_{max} , and CV. An RD within $\pm 5\%$ was considered a tolerable quantitative deviation [97–99]. For sparse DDBs, the bias with the greatest absolute magnitude among the five random seeds was used. For clustered DDBs, the bias with the greatest absolute magnitude among the 12 positions was used. The fraction of lesion VOIs remaining within the $\pm 5\%$ threshold was additionally determined.

In the simulated 40-cm phantom, cylindrical VOIs 10 mm in diameter and 10 mm in length were arranged in concentric rings from the centre to the periphery while

maintaining a 15-mm margin from the phantom boundary. The 10-mm VOIs were used to approximate small-lesion quantification. Mean activity concentration was extracted from reference and DDB-affected images, and RDs were mapped spatially. VOIs exceeding the $\pm 5\%$ threshold were defined as affected regions, and their cumulative volume was expressed relative to the total phantom volume. Phantom analyses were repeated across activity concentrations and defect configurations to evaluate dependence on count statistics and spatial propagation of DDB-related bias. Illustrations of lesion distributions in representative patients and of phantom-based VOI placement are shown in **Figure 13**.

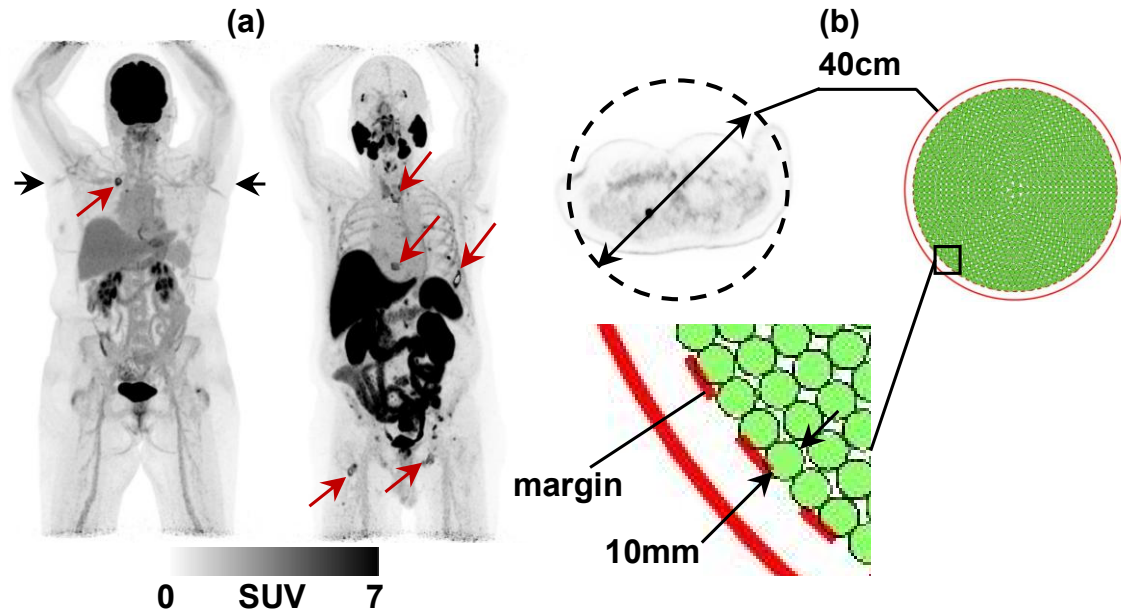


Figure 13 Patient lesion distributions and phantom volume-of-interest placement for detector-block-defect analysis. (a) Maximum-intensity projection images of representative patients undergoing $[^{18}\text{F}]\text{FDG}$ and $[^{18}\text{F}]\text{PSMA-1007}$ PET/CT; arrows indicate representative segmented lesions used for quantitative analysis. (b) Transaxial size comparison between a patient image and a 40-cm-diameter cylindrical phantom. Cylindrical volumes of interest (diameter $\text{Ø} = 10$ mm, length $L = 10$ mm) were arranged in concentric rings with a minimum 15-mm margin from the phantom boundary.

4 Results

4.1 Optimisation of an Abbreviated [^{18}F]FDG Dynamic Protocol for Parametric Imaging

IDIFs derived from the HS and UHS reconstructions showed negligible differences (Figure 14 [59]). Across the 6 patients, the relative bias in the IDIF area under the curve was $-0.7 \pm 0.4\%$, indicating that both sensitivity modes provided essentially equivalent input functions for the evaluated 65-min dynamic acquisition.

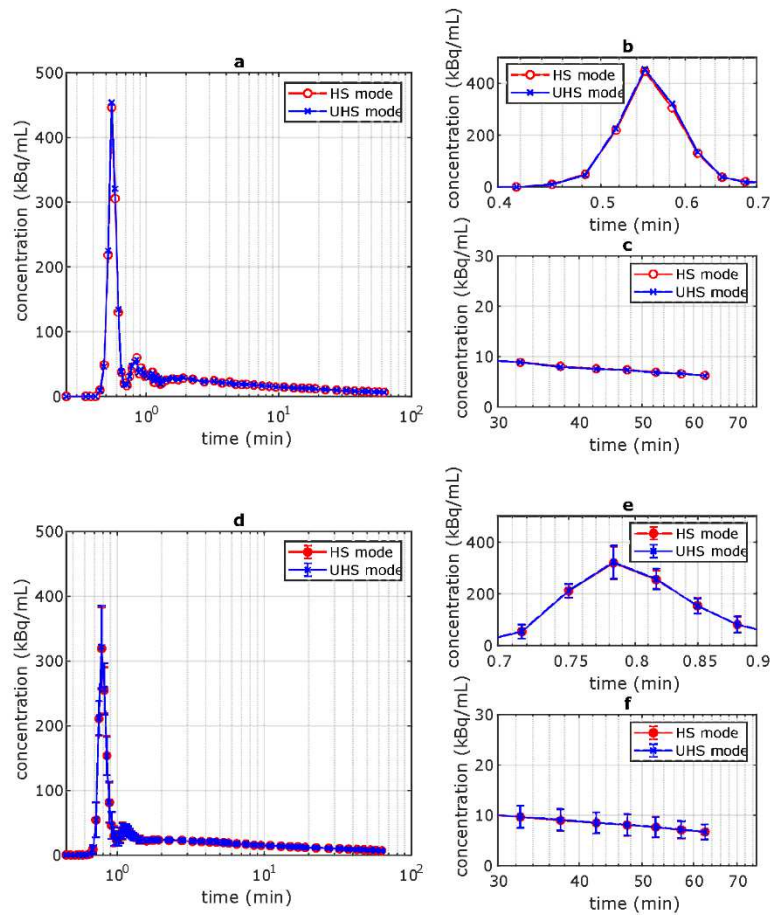


Figure 14 Patient-specific image-derived input functions in high- and ultra-high sensitivity PET acquisition modes. (a) Representative IDIFs in high sensitivity (HS) and ultra-high sensitivity (UHS) modes. (b) Enlarged view of the peak region for the representative IDIFs. (c) Enlarged view from 30 to 65 min post-injection. (d) Mean IDIFs from 6 patients in HS and UHS modes. (e) Enlarged view of the mean IDIF peak region. (f) Enlarged view of the mean IDIF from 30 to 65 min post-injection [59].

For IDIF-based direct Patlak reconstruction, the number of Patlak frames did not

significantly affect Ki or DV. UHS mode produced lower bias and higher precision than HS mode for both parameters (Ki, $p < 0.001$; DV, $p < 0.001$). Complete bias and precision statistics for Ki and DV from IDIF-based direct Patlak reconstruction are reported in **Table 2** [59].

Table 2 Bias and precision of Ki and DV estimates from patient-specific IDIF-based direct Patlak reconstruction. Ki and DV estimates reconstructed with 5 or 6 Patlak frames are compared with the four-frame reference for the same sensitivity mode using $t^* = 45$ min. Values are reported as mean bias $\pm$ precision in percent. Ki = net influx rate constant; DV = distribution volume; HS = high sensitivity; UHS = ultra-high sensitivity [59].

number of Patlak frames	sensitivity mode	bias $\pm$ precision (Ki)	bias $\pm$ precision (DV)
5	HS	$-1.9 \pm 2.7\%$	$2.7 \pm 4.1\%$
	UHS	$-0.3 \pm 1.6\%$	$-0.1 \pm 2.8\%$
6	HS	$-1.1 \pm 2.4\%$	$0.8 \pm 3.7\%$
	UHS	$-0.1 \pm 1.8\%$	$-0.5 \pm 2.5\%$

When an sPBIF was used, the 45–65 min window provided the most reliable compromise between scan duration and quantitative accuracy, as shown in **Supplementary Table 1** [59]. In UHS mode, four Patlak frames yielded a Ki bias and precision of $2.7 \pm 3.4\%$ and a DV bias and precision of $18.1 \pm 7.5\%$. Increasing the Patlak start time t^* degraded the estimates. With four Patlak frames in UHS mode, Ki bias and precision degraded from $2.7 \pm 3.4\%$ at $t^* = 45$ min to $15.0 \pm 10.5\%$ at $t^* = 50$ min and $34.5 \pm 22.5\%$ at $t^* = 55$ min. DV bias and precision changed from $18.1 \pm 7.5\%$ ($t^* = 45$ min) to $2.6 \pm 13.9\%$ ($t^* = 50$ min) and $-29.2 \pm 17.3\%$ ($t^* = 55$ min). A comprehensive comparison is shown in **Figure 15** [59].

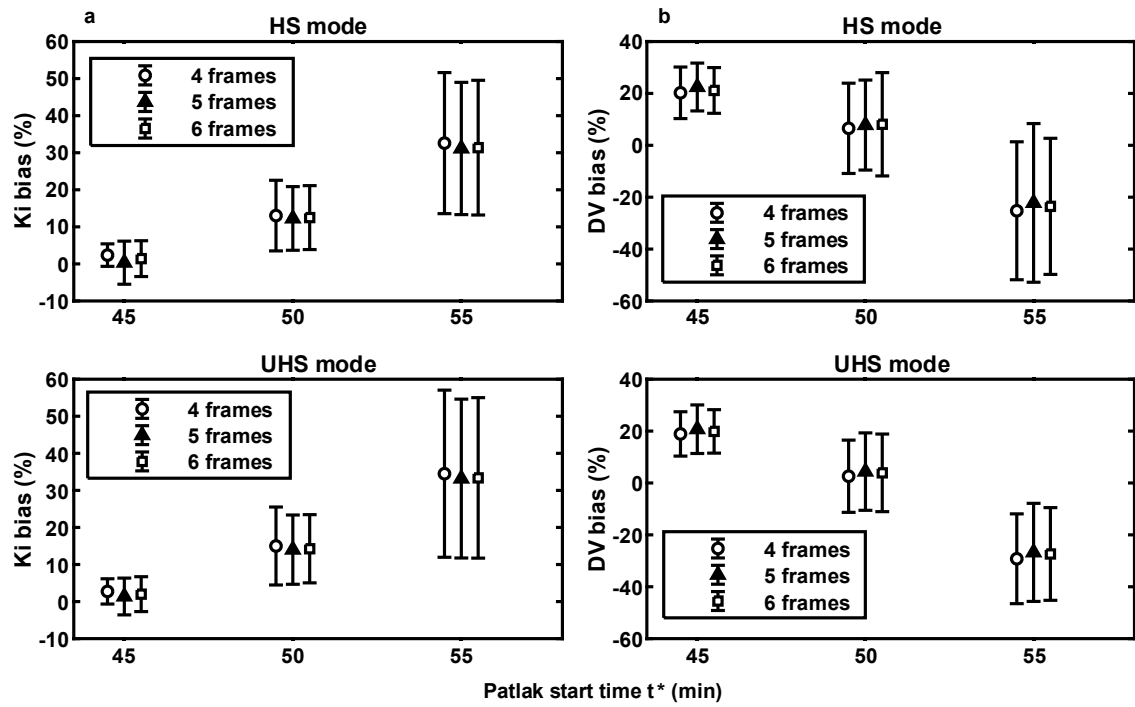


Figure 15 Bias and precision of direct Patlak Ki and DV estimates using scaled population-based input functions. (a) Ki bias and precision and (b) DV bias and precision are shown for high sensitivity (HS) and ultra-high sensitivity (UHS) modes, for 4, 5, or 6 Patlak frames, and for Patlak start times $t^* = 45, 50,$ and 55 min. Values are expressed as percentages relative to patient-specific image-derived input function (IDIF)-based estimates reconstructed with the same settings; points show mean bias, and error bars show precision. Precision denotes the standard deviation of relative bias. Ki = net influx rate constant; DV = distribution volume [59].

Visual comparisons showed higher TBRs in Ki images than in SUV images (**Figure 16** [59]).

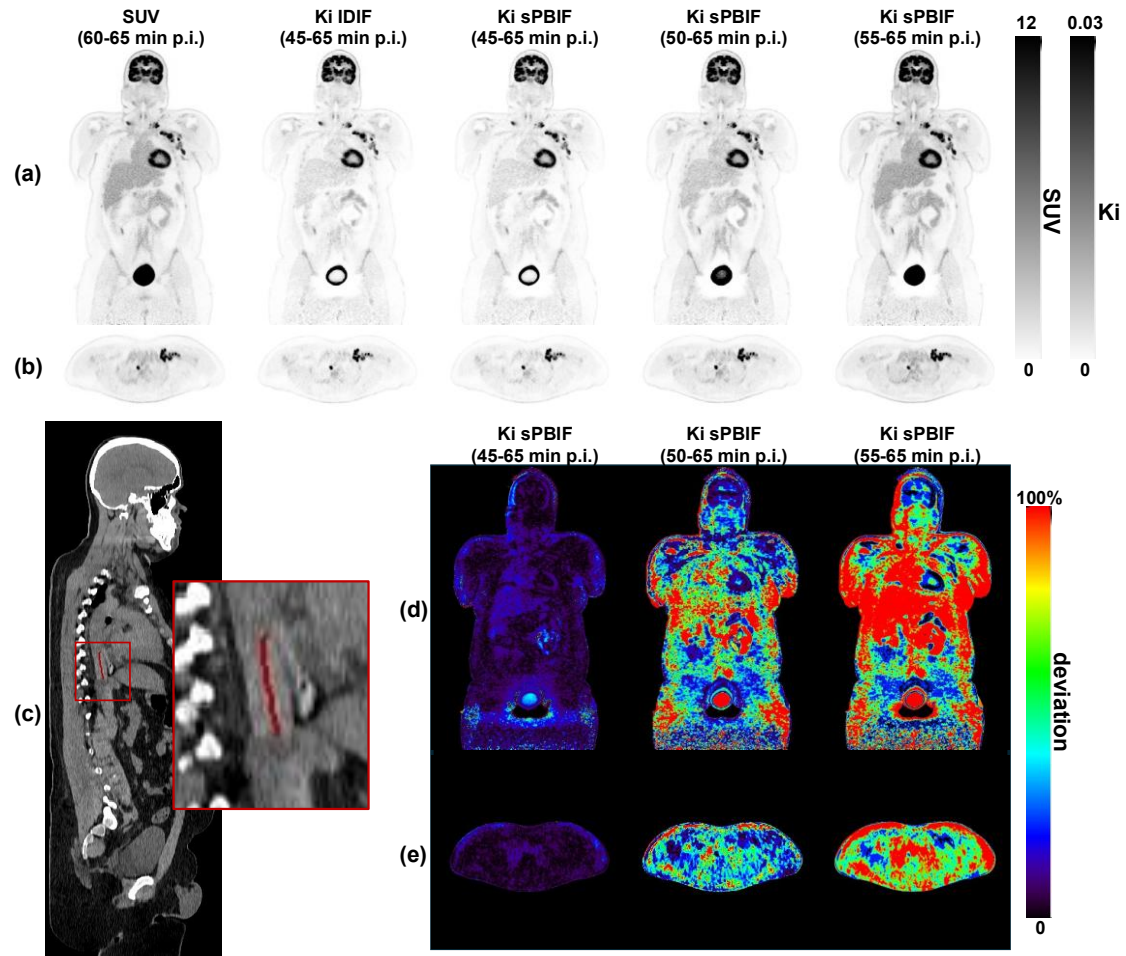


Figure 16 Representative SUV and Ki images for abbreviated direct Patlak protocols in ultra-high-sensitivity mode. (a, b) Coronal and transaxial views of SUV and direct Patlak Ki images reconstructed using an IDIF or an sPBIF over the indicated post-injection windows. (c) Sagittal computed tomography (CT) image and magnified view showing the 1.68-cm³ thoracic-aorta volume of interest used to derive the image-derived input function (IDIF) with SnakeVOI. (d, e) Coronal and transaxial absolute relative-difference maps for Ki estimates relative to the patient-specific IDIF reference ($t^* = 45$ min, 45–65 min p.i.). Ki = net influx rate constant in units of (mL/cm³/min); sPBIF = scaled population-based input function [59].

In UHS mode, the TBR was 17.2 ± 9.6 for direct Patlak Ki images reconstructed using the patient-specific IDIF, compared with 6.2 ± 3.1 for SUV images. With sPBIF-based Ki images, the TBR was 20.2 ± 12.0 for the 45–65 min window and decreased with shorter windows, reaching 6.9 ± 3.5 for 55–65 min. A complete statistical summary of TBRs for both SUV and parametric images is provided in **Table 3** [59].

Table 3 Tumour-to-background ratios (TBRs) for SUV and [^{18}F]FDG parametric images. TBR was calculated for SUV images and Ki images reconstructed by direct Patlak analysis using a patient-specific IDIF or an sPBIF in high-sensitivity and ultra-high-sensitivity mode. Ki = net influx rate constant; IDIF = image-derived input function; sPBIF = scaled population-based input function; p.i. = post-injection; t^* = Patlak start/equilibration time [59].

image/protocol	input function	HS mode	UHS mode
SUV (60–65 min p.i.)	--	6.4 ± 3.1	6.2 ± 3.1
Ki (45–65 min p.i. $t^* = 45$ min)	IDIF	18.0 ± 9.0	17.2 ± 9.6
	sPBIF	21.3 ± 11.5	20.2 ± 12.0
Ki (50–65 min p.i. $t^* = 50$ min)	sPBIF	11.2 ± 5.6	10.6 ± 5.4
Ki (55–65 min p.i. $t^* = 55$ min)	sPBIF	7.2 ± 3.5	6.9 ± 3.5

The close agreement between IDIF- and sPBIF-based Ki images for the 45–65 min protocol was supported by low image-level deviations. In UHS mode, the absolute RD for Ki was $0.8 \pm 0.3\%$, and the PSNR was 75.7 ± 4.1 dB. Shortening the scan window increased deviations. In HS mode, the absolute RD for Ki increased from $0.8 \pm 0.4\%$ at 45–65 min to $7.3 \pm 2.4\%$ at 50–65 min and $19.2 \pm 5.8\%$ at 55–65 min. Corresponding values for DV increased from $1.6 \pm 0.8\%$ to $6.6 \pm 2.9\%$ and $13.7 \pm 6.3\%$. Sensitivity mode had little effect on image similarity metrics for the same t^* value. **Table 4** [59] provides RD, SSIM, and PSNR statistics for [^{18}F]FDG Ki and DV images generated using sPBIF, with the IDIF-based images serving as the reference.

Table 4 Whole-body image-level agreement between sPBIF- and IDIF-based [^{18}F]FDG Patlak images. Signed relative difference (RD), absolute RD, structural similarity index measure (SSIM), and peak signal-to-noise ratio (PSNR) are reported for Ki and DV images reconstructed using sPBIF relative to the patient-specific IDIF reference. Ki = net influx rate constant; DV = distribution volume; HS = high sensitivity; UHS = ultra-high sensitivity; p.i. = post-injection [59].

		sensitivity mode	RD (%)	absolute RD (%)	SSIM	PSNR (dB)
Ki	45–65 min p.i.	HS	0.2 ± 0.2	0.8 ± 0.4	0.999 ± 0.001	75.5 ± 3.9
		UHS	0.3 ± 0.3	0.8 ± 0.3	0.999 ± 0.001	75.7 ± 4.1
	50–65 min p.i.	HS	6.8 ± 2.4	7.3 ± 2.4	0.999 ± 0.001	64.5 ± 3.2
		UHS	6.9 ± 2.3	7.5 ± 2.5	0.999 ± 0.001	64.5 ± 3.3
	55–65 min p.i.	HS	18.6 ± 5.7	19.2 ± 5.8	0.997 ± 0.002	59.0 ± 2.7
		UHS	19.1 ± 6.1	19.7 ± 6.2	0.997 ± 0.002	59.2 ± 2.7
DV	45–65 min p.i.	HS	1.5 ± 0.9	1.6 ± 0.8	0.997 ± 0.002	73.1 ± 9.8
		UHS	1.4 ± 0.7	1.5 ± 0.7	0.997 ± 0.002	72.4 ± 9.0
	50–65 min p.i.	HS	0.4 ± 3.6	6.6 ± 2.9	0.953 ± 0.027	61.7 ± 11.4
		UHS	0.1 ± 3.1	6.3 ± 2.4	0.956 ± 0.026	61.2 ± 10.6
	55–65 min p.i.	HS	0.2 ± 7.4	13.7 ± 6.3	0.898 ± 0.036	56.6 ± 10.7
		UHS	-0.1 ± 6.8	13.6 ± 5.7	0.903 ± 0.035	56.0 ± 9.7

Taken together, these findings supported the 45–65 min, four-frame, sPBIF-based direct Patlak protocol as a clinically suitable abbreviated protocol for subsequent NSCLC imaging under the investigated conditions. The 50–65 and 55–65 min windows produced progressively larger deviations and lower image fidelity.

4.2 Clinical Application in NSCLC: Tumour Subtype and PD-L1

Associations

The optimised abbreviated protocol was then applied to 51 treatment-naïve patients with histopathologically confirmed NSCLC. The interval between tissue sampling and [^{18}F]FDG PET/CT was 28.6 ± 31.0 days. The patient cohort characteristics are reported in **Table 5**. TPS values in PD-L1-positive tumours did not differ between LUAD and LUSC ($45.8 \pm 31.1\%$ versus $37.3 \pm 32.6\%$; $p = 0.58$).

Table 5 Demographic and histopathological characteristics of the non-small cell lung cancer study cohort. Values are reported as mean $\pm$ standard deviation for age and as n (%) or n/n for categorical variables, as shown. PD-L1 status is reported within each histological subtype. PD-L1 = programmed death-ligand 1; n = number of patients.

characteristic	value
Age (years)	72 ± 8.3
male/female	33/18
biopsy/cytology site: lung / lymph node / other	46 (90.1%) / 4 (7.8%) / 1 (2.1%)
adenocarcinoma: total / PD-L1 negative / PD-L1 positive	34 (66.6%) / 12 (35.3%) / 22 (64.7%)
squamous cell carcinoma: total / PD-L1 negative / PD-L1 positive	17 (33.3%) / 8 (47.1%) / 9 (52.9%)

4.2.1 Deviations in Parametric Values between HS and UHS Modes across

Lesion Axial Positions

116 tumour lesions were delineated from a total of 56 patients, including 50 of the 51 NSCLC confirmed patients and 6 additional patients from the excluded patient cohort. The axial position of each lesion was measured using the centre of the axial field of view as the spatial reference point. 81% of the lesions were located at axial offsets of ≥ 10 cm. The histogram of the lesion axial-position distribution is shown in **Figure 17**.

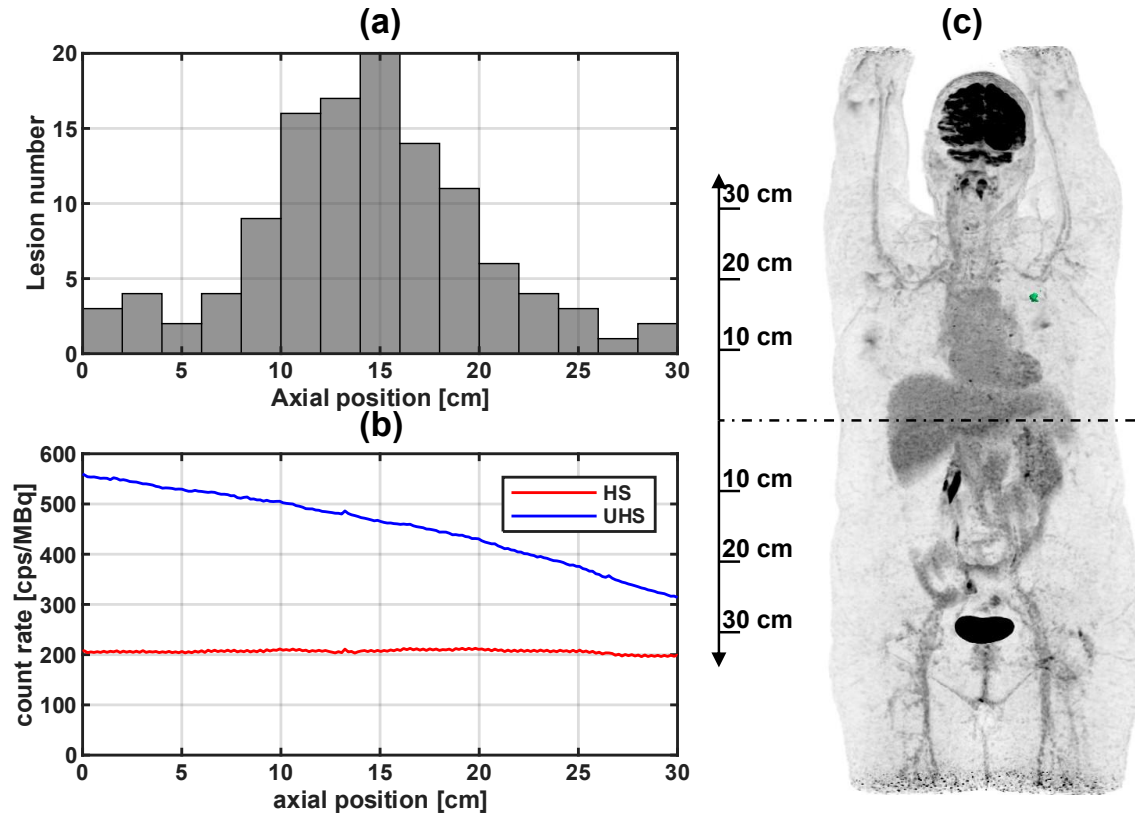


Figure 17 Lesion axial-position distribution in the selected patient cohort. (a) Histogram of delineated lesion axial positions relative to the centre of the scanner axial field of view. (b) Enlarged axial sensitivity profiles measured according to the National Electrical Manufacturers Association (NEMA) NU 2-2018 standard. (c) Representative maximum-intensity projection illustrating the axial-position reference, with the scanner centre set to 0 cm and distances marked at 10, 20, and 30 cm.

To quantify the effect of sensitivity mode on SUV_{mean} , KI_{mean} , and DV_{mean} , the RDs were plotted as a function of lesion axial position in **Figure 18**. The mean RDs were $-3.6 \pm 3.0\%$ (SUV_{mean}), $-3.8 \pm 6.6\%$ (KI_{mean}) and $-2.4 \pm 37.2\%$ (DV_{mean}). No statistically significant correlation was found between lesion axial position and any of the quantitative metrics ($p = 1.00$).

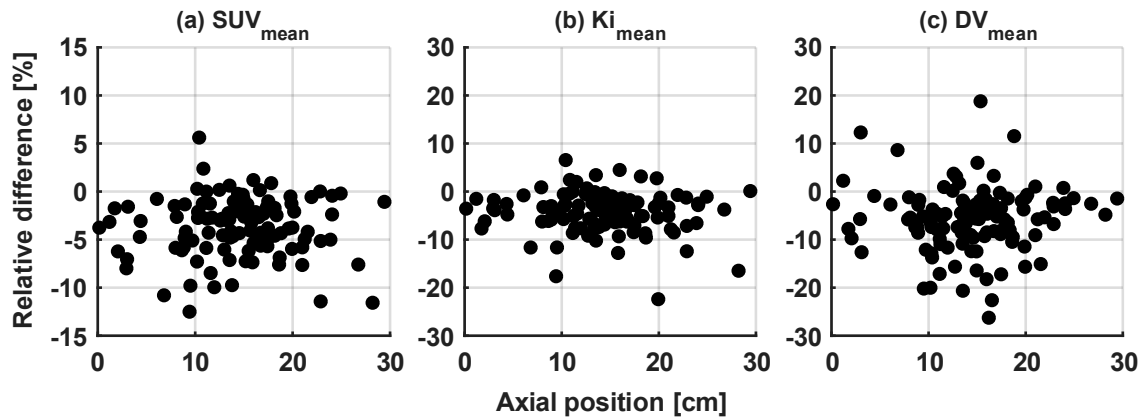


Figure 18 Relative differences in lesion quantitative metrics between high- and ultra-high-sensitivity modes as a function of lesion axial position. Scatter plots show relative differences for (a) SUV_{mean} , (b) Ki_{mean} , and (c) DV_{mean} . Ki = net influx rate constant; DV = distribution volume.

4.2.2 Associations of SUV, Ki, and DV with Tumour Subtype and PD-L1 Status

97 tumour lesions from 51 NSCLC confirmed patients were analysed, including 66 LUAD lesions and 31 LUSC lesions (**Figure 19**).

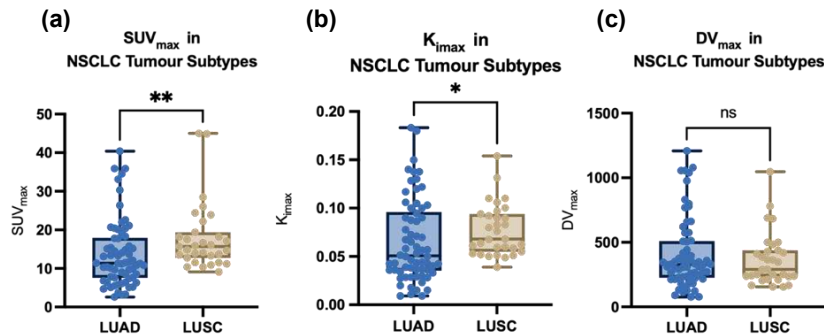


Figure 19 SUV_{max} , Ki_{max} , and DV_{max} by non-small cell lung cancer tumour (NSCLC) subtype. Boxplots compare (a) SUV_{max} , (b) Ki_{max} , and (c) DV_{max} between lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) lesions. Boxes show the interquartile range, centre lines show medians, whiskers show $1.5 \times$ interquartile range, and points represent individual lesions. Mann–Whitney U tests were used; exact p-values were SUV_{max} $p = 0.003$, Ki_{max} $p = 0.001$, and DV_{max} $p = 0.75$. ns = non-significant.

LUSC lesions showed higher SUV_{max} than LUAD lesions (17.9 ± 8.6 versus 13.7 ± 8.7 ; $p = 0.003$) and higher Ki_{max} (0.07 ± 0.02 versus 0.06 ± 0.04 ; $p = 0.001$). DV_{max} did not differ between histological subtypes ($p = 0.75$). No statistically significant differences

were observed between primary tumours and metastatic lesions in SUV or parametric values within either subtype.

When lesions were stratified by PD-L1 status, PD-L1-positive lesions had higher $K_{i_{\max}}$ (0.076 ± 0.04 versus 0.050 ± 0.02 ; $p = 0.02$) and $DV_{\max}$ (441.0 ± 280.0 versus 296.4 ± 149.9 ; $p = 0.02$) than PD-L1-negative lesions. $SUV_{\max}$ was higher in PD-L1-positive lesions but did not reach the conventional threshold for statistical significance (16.6 ± 9.7 versus 11.7 ± 5.5 ; $p = 0.051$). The comparisons are shown in **Figure 20**.

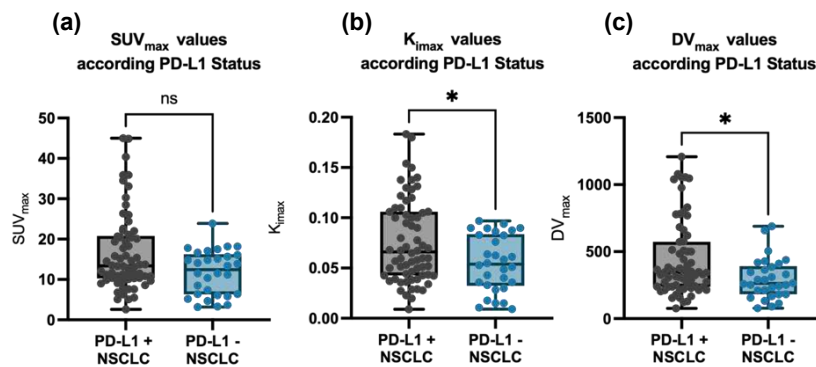


Figure 20 $SUV_{\max}$, $K_{i_{\max}}$, and $DV_{\max}$ by PD-L1 status in non-small cell lung cancer lesions. Boxplots compare (a) $SUV_{\max}$, (b) $K_{i_{\max}}$, and (c) $DV_{\max}$ between PD-L1-positive and PD-L1-negative lesions. PD-L1 positivity was defined as tumour proportion score $\geq 1\%$. Boxes show the interquartile range, centre lines show medians, whiskers show $1.5 \times$ interquartile range, and points represent individual lesions. Mann–Whitney U tests were used; exact p-values were $SUV_{\max}$ $p = 0.051$, $K_{i_{\max}}$ $p = 0.02$, and $DV_{\max}$ $p = 0.02$. PD-L1 = programmed death-ligand 1; ns = non-significant.

4.3 Respiratory Motion Correction: Patient Observations and Digital-Twin Validation

4.3.1 Clinical Impact of Respiratory Motion Correction

Representative examples of respiratory motion correction are shown in **Figure 21**.

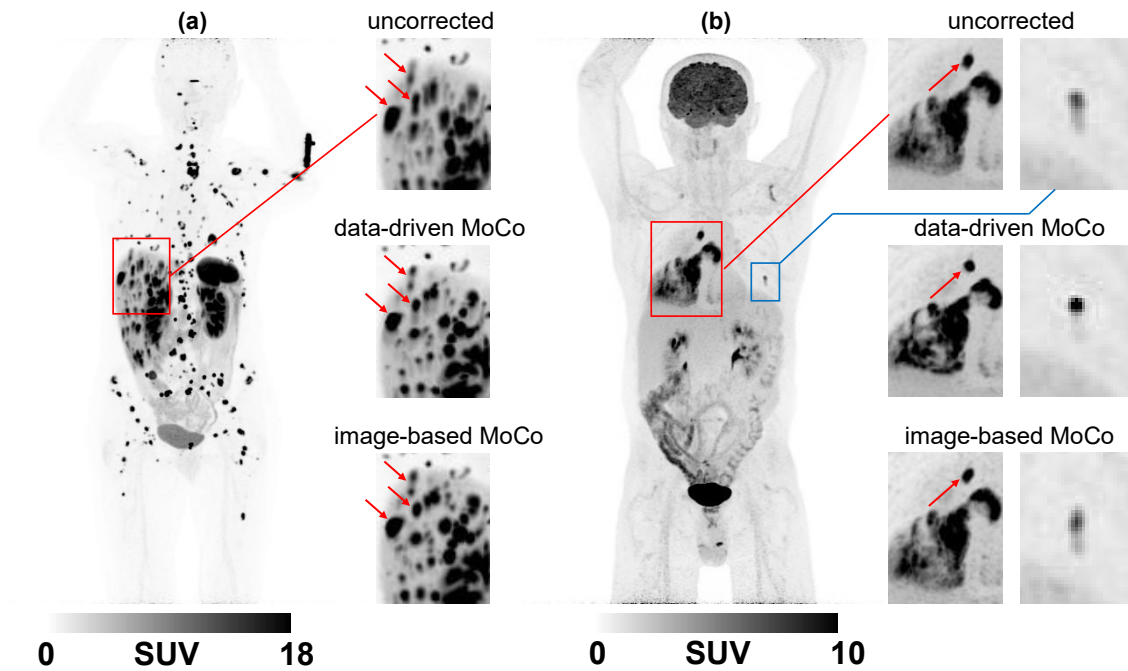


Figure 21 Respiratory motion correction in representative clinical PET/CT examinations. Maximum-intensity projection images and enlarged lesion views are shown for (a) $[^{18}\text{F}]\text{SiFalin-TATE}$ and (b) $[^{18}\text{F}]\text{FDG}$ PET/CT. For each tracer, uncorrected images are compared with data-driven motion correction (OncoFreeze AI) and image-based motion correction (FALCON). Arrows indicate hepatic or pulmonary lesions affected by respiratory motion, and enlarged views demonstrate changes in lesion blurring and delineation after correction. MoCo = motion correction.

Respiratory motion resulted in visible lesion blurring and elongation, particularly for hepatic and peripheral pulmonary lesions adjacent to the diaphragm. Both motion-correction strategies visibly reduced motion-induced blurring and restored lesion conspicuity. The data-driven method generally produced sharper lesion boundaries and a more compact lesion appearance than the image-based method.

Image noise was assessed using the CV. In the patient datasets, CV increased from $9.5 \pm 1.5\%$ in uncorrected images to $10.3 \pm 1.6\%$ after data-driven correction and $11.4 \pm 2.0\%$ after image-based correction.

Across 20 patients, 135 lesions were analysed, including 71 in the liver, 36 in the lower lung, and 28 in the upper lung. The largest correction-induced changes were consistently observed for liver lesions, for which data-driven motion correction resulted in

substantially larger increases in SUV_{mean} than did image-based motion correction ($48.1 \pm 18.9\%$ versus $17.0 \pm 12.0\%$, $p < 0.01$, **Figure 22(a-1),(b-1)**).

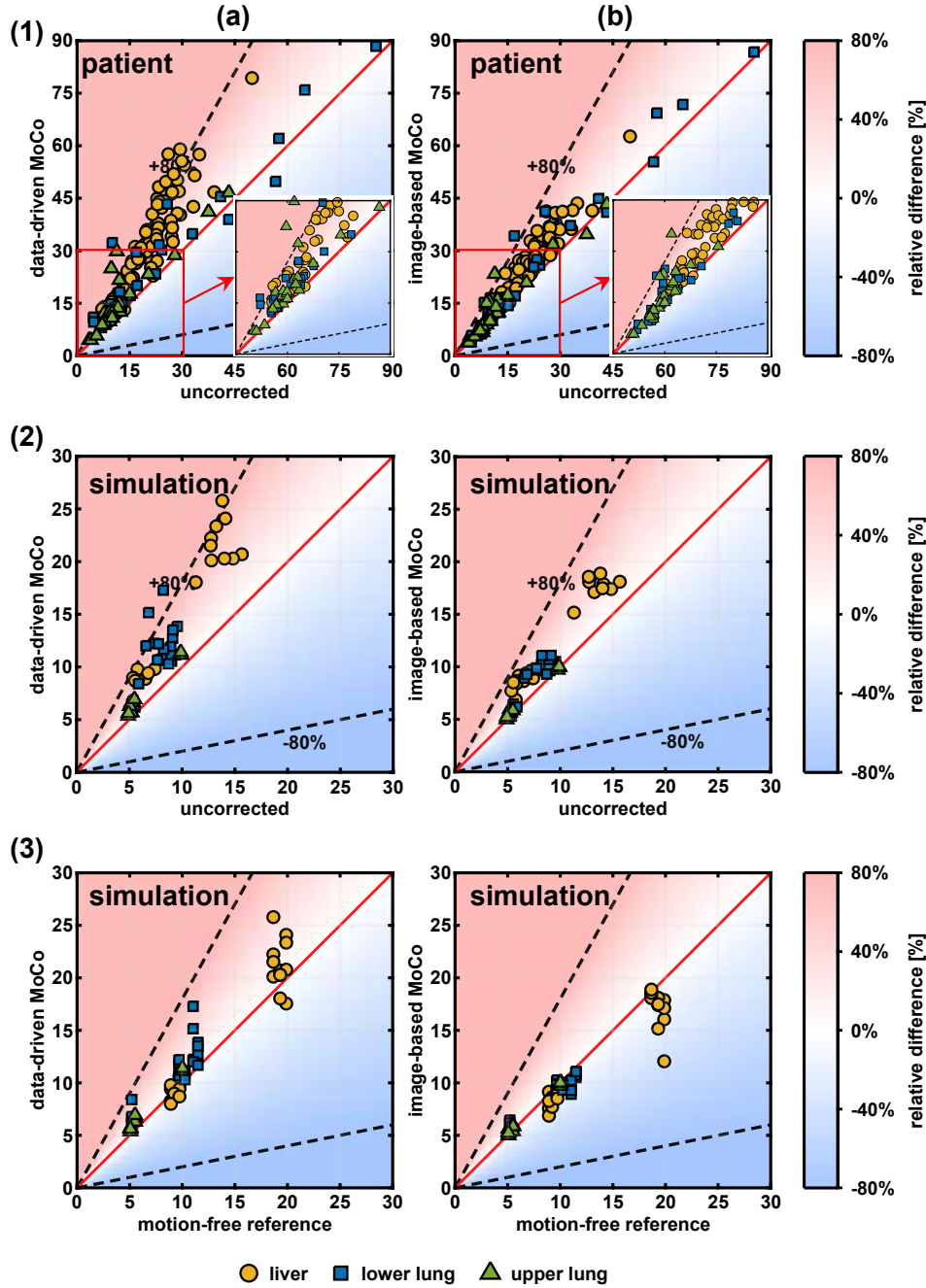


Figure 22 Lesion SUV_{mean} changes after respiratory motion correction in patient and simulated phantom datasets. Row 1 compares data-driven (a) and image-based (b) motion-corrected patient values with corresponding uncorrected values. Row 2 shows the same comparison in the patient-like phantom. Row 3 compares phantom motion-corrected values with the motion-free reference. Dashed lines indicate $\pm 80\%$ relative difference. Circles, squares, and triangles denote liver, lower-lung, and upper-lung lesions, respectively. MoCo = motion correction.

Because motion-free reference images were not available for the patient datasets, the patient-like phantom data were used to evaluate whether these correction trends were reproducible under controlled conditions. Correction-induced RDs in the phantom, calculated relative to the uncorrected images, showed the same overall direction as the patient results, with SUV recovery and MTV reduction after motion correction. For example, liver SUV_{mean} increased by $55.3 \pm 16.1\%$ after data-driven correction and by $34.5 \pm 11.7\%$ after image-based correction ($p = 0.01$), as shown in the scatter plots in **Figure 22(a-2),(b-2)**. Complete patient and phantom relative-difference statistics are provided in **Supplementary Table 2**.

A similar trend was observed for lower-lung lesions ($32.5 \pm 21.2\%$ versus $16.3 \pm 15.6\%$, $p = 0.06$), whereas upper-lung lesions exhibited the smallest change ($28.4 \pm 32.0\%$ versus $10.4 \pm 17.2\%$, $p < 0.01$). Comparable findings were observed for SUV_{max} (**Supplementary Figure 1(a-1),(b-1)**).

MTV consistently decreased more after data-driven than after image-based motion correction (**Figure 23(a-1),(b-1)**), indicating stronger recovery of lesion boundaries. Complete quantitative results are provided in **Supplementary Table 2**.

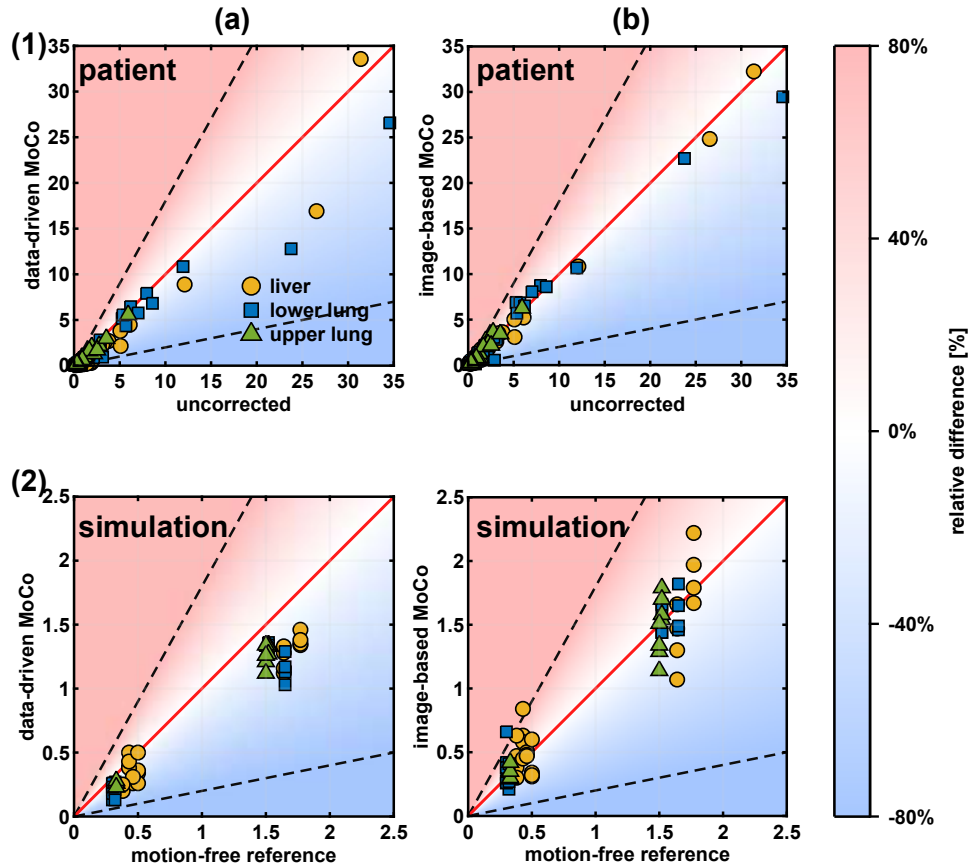


Figure 23 Metabolic tumour volume (MTV) changes after respiratory motion correction. Scatter plots compare lesion MTV after data-driven (a) and image-based (b) motion correction with uncorrected values in clinical datasets (row 1) and with the motion-free reference in simulated datasets (row 2). Dashed lines indicate $\pm 80\%$ relative difference. Circles, squares, and triangles denote liver, lower-lung, and upper-lung lesions, respectively. MTV is reported in millilitres; MoCo = motion correction.

The patient-like phantom reproduced the qualitative and quantitative findings observed in the clinical datasets. Representative simulated images demonstrated the same respiratory motion-induced lesion blurring, predominantly in the craniocaudal direction, followed by comparable lesion sharpening after both data-driven and image-based motion correction (**Figure 9(c)**).

Image noise showed the same behaviour as in the clinical datasets. The CV changed negligibly among the motion-free reference (8.8%), uncorrected images ($8.7 \pm 0.1\%$), and data-driven motion correction ($9.5 \pm 0.4\%$), whereas image-based motion correction

resulted in the highest image noise ($11.9 \pm 0.5\%$).

Quantitative analysis reflected the clinical findings. The largest correction-induced changes were again observed for liver lesions, followed by lower-lung lesions, whereas upper-lung lesions showed only minor changes. Data-driven motion correction consistently produced larger correction-induced changes than image-based motion correction for SUV_{mean} (**Figure 22**), SUV_{max} (**Supplementary Figure 1**), and MTV (**Figure 23**). Complete quantitative results are summarised in **Supplementary Table 2**.

4.3.2 Lesion Recovery and Residual Error After Motion Correction Relative to the Motion-Free Reference

Relative to the motion-free reference, respiratory motion introduced substantial quantitative errors that were strongly location-dependent. The largest SUV underestimation occurred in liver lesions, where SUV_{mean} was reduced by $31.2 \pm 6.8\%$, followed by lower-lung lesions ($15.5 \pm 13.9\%$), whereas upper-lung lesions were only minimally affected ($2.5 \pm 2.7\%$) (**Figure 22(a-3),(b-3)**). These simulations indicated that respiratory motion predominantly affected anatomical regions adjacent to the diaphragm. Both motion-correction strategies reduced these motion-induced errors. For liver lesions, data-driven motion correction reduced the SUV_{mean} error from $-31.2 \pm 6.8\%$ to $4.3 \pm 11.7\%$, whereas image-based motion correction reduced the error to $-10.0 \pm 9.2\%$ ($p = 0.01$), indicating that the stronger correction achieved by the data-driven approach resulted in quantitative values closer to the motion-free reference. In contrast, for lower- and upper-lung lesions, data-driven motion correction tended to overcorrect, resulting in SUV_{mean} errors of $19.8 \pm 16.3\%$ and $14.5 \pm 5.3\%$, respectively, whereas image-based motion correction remained closer to the motion-free reference ($-1.6 \pm 10.2\%$ and $3.0 \pm 4.4\%$). Similar regional behaviour was observed for SUV_{max} (**Supplementary Figure 1**), demonstrating that the relative performance of both correction strategies depended on lesion location.

For MTV, respiratory motion resulted in substantial overestimation of lesion volume, particularly for liver lesions ($57.4 \pm 82.5\%$). Both correction methods reduced these errors. Although image-based motion correction produced MTV values that were closer to the motion-free reference on average, this was accompanied by considerably larger variability across lesions. In contrast, data-driven motion correction yielded more consistent MTV recovery (standard deviations of 15.6% and 13.6% for liver and lower-lung lesions, respectively), although with an overcorrection tendency (mean errors of -25.2% and -26.6%). Complete quantitative results are summarised in **Table 6**.

Table 6 Signed relative error of phantom quantitative metrics after respiratory motion correction relative to the motion-free reference. The table compares uncorrected, data-driven motion-corrected, and image-based motion-corrected images for SUV_{mean} , SUV_{max} , and metabolic tumour volume (MTV) in liver, lower-lung, and upper-lung lesions. p-values compare data-driven and image-based motion-correction errors within each structure. MoCo = motion correction.

parameter	structure	uncorrected (%)	data-driven MoCo (%)	image-based MoCo (%)	p-value
SUV_{mean} (phantom)	liver	-31.2 ± 6.8	4.3 ± 11.7	-10.0 ± 9.2	0.01
	lower lung	-15.5 ± 13.9	19.8 ± 16.3	-1.6 ± 10.2	0.02
	upper lung	-2.5 ± 2.7	14.5 ± 5.3	3.0 ± 4.4	0.06
SUV_{max} (phantom)	liver	-27.2 ± 7.7	8.6 ± 13.1	-4.8 ± 10.6	0.02
	lower lung	-11.8 ± 14.3	24.0 ± 17.3	2.7 ± 11.0	0.01
	upper lung	-2.5 ± 5.3	18.2 ± 5.0	8.0 ± 9.7	0.12
MTV (phantom)	liver	57.4 ± 82.5	-25.2 ± 15.6	6.6 ± 31.4	0.01
	lower lung	14.0 ± 26.6	-26.6 ± 13.6	8.3 ± 31.1	0.06
	upper lung	6.3 ± 9.1	-17.7 ± 5.8	-0.1 ± 14.1	0.10

To assess the robustness of both motion correction strategies under different breathing conditions, quantitative recovery was evaluated for the two patient-derived respiratory patterns (pattern-1 and pattern-2; **Figure 9(b)**) and for respiratory motion amplitudes of 2 cm and 3 cm (**Figure 24**).

Respiratory pattern had only a minor influence on quantitative recovery. In the uncorrected datasets, SUV_{mean} errors were comparable for both respiratory patterns

(pattern-1: $-17.7 \pm 16.3\%$; pattern-2: $-19.2 \pm 13.2\%$; $p = 0.70$). After data-driven motion correction, residual errors remained comparable for both respiratory patterns ($12.6 \pm 18.7\%$ versus $11.5 \pm 8.1\%$; $p = 0.79$), and no significant respiratory-pattern dependence was observed after image-based motion correction.

In contrast, respiratory motion amplitude substantially affected quantitative recovery. Without motion correction, SUV_{mean} underestimation increased significantly from $-16.1 \pm 12.8\%$ at a 2-cm amplitude to $-21.0 \pm 16.1\%$ at a 3-cm amplitude ($p = 0.02$). Following data-driven motion correction, quantitative recovery remained largely independent of motion amplitude ($12.6 \pm 11.9\%$ versus $11.4 \pm 16.5\%$; $p = 0.21$). In contrast, image-based motion correction showed increasing residual underestimation with larger motion amplitudes ($-2.0 \pm 8.9\%$ versus $-6.5 \pm 11.0\%$; $p < 0.01$), indicating greater sensitivity to increasing respiratory motion.

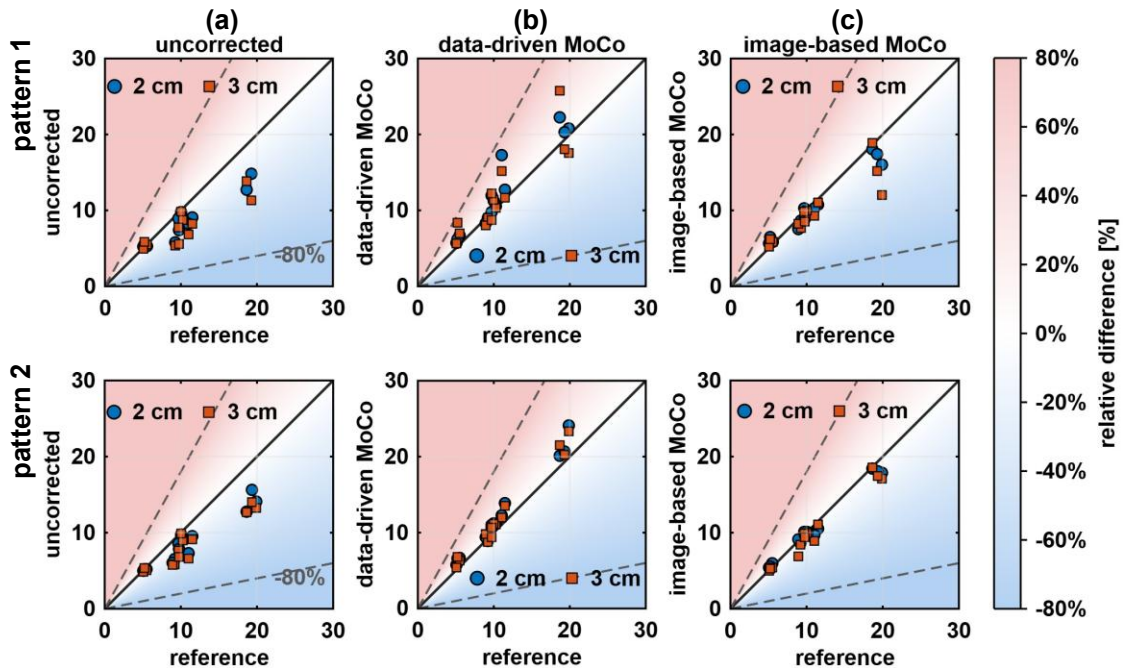


Figure 24 Phantom SUV_{mean} relative to the motion-free reference under different respiratory motion patterns and amplitudes. Rows show respiratory patterns 1 and 2. Columns show (a) uncorrected images, (b) data-driven motion correction, and (c) image-based motion correction. Dashed lines indicate $\pm 80\%$ relative difference. Blue circles and orange squares indicate maximum respiratory amplitudes of 2 cm and 3 cm, respectively. MoCo = motion correction.

4.4 System Robustness: Patient Quantification and Phantom Analysis

4.4.1 Patient Qualitative and Quantitative Assessment of DDB Configurations and Mitigation Strategies

In patient images reconstructed with the HighRes protocol and HS mode (HighRes-HS), simulated sparse DDBs did not produce visually apparent global image degradation, even with large numbers of DDBs, as shown in **Figure 25**. Relative-difference maps, however, revealed increasing local noise and localised SUV biases as the number of DDBs increased. These effects were pronounced close to the scanner-bore wall. A clustered 16-DDB defect, corresponding to a full DEA, produced larger zones of SUV bias across the transaxial field of view at the axial location of the DDBs. CV was affected by both sparse and clustered defects, exceeding the $\pm 5\%$ threshold at 32 or more sparse DDBs (**Figure 26(c)**), whereas clustered defects had a larger effect and increased CV by 14.8%.

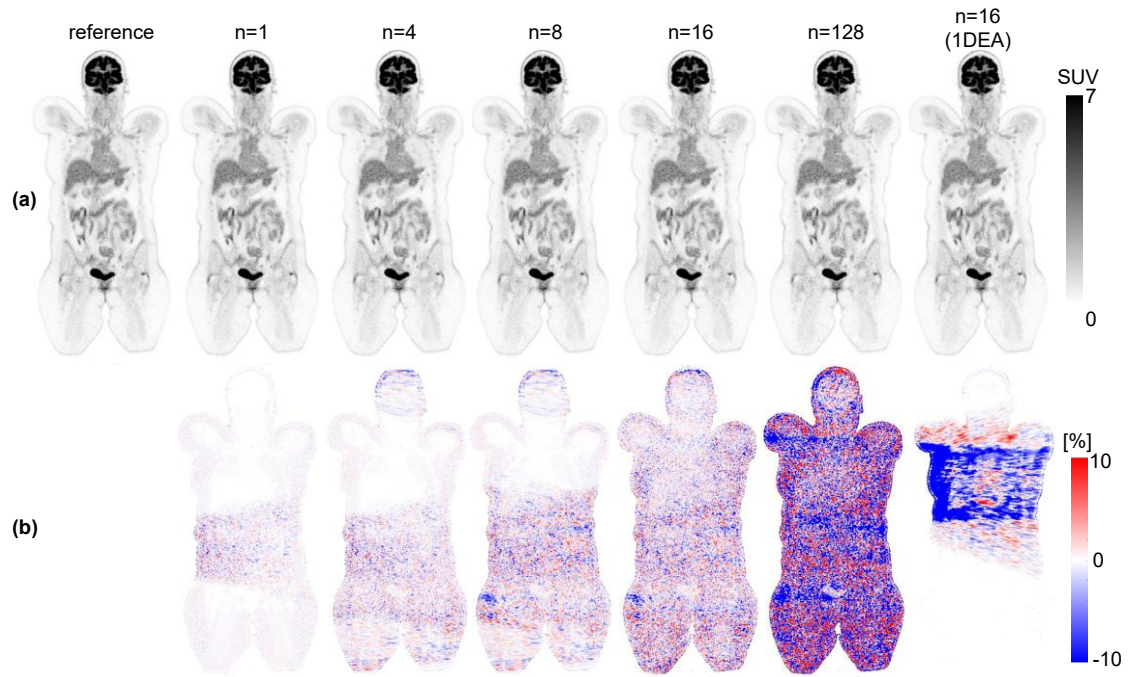


Figure 25 Impact of simulated defective detector blocks (DDBs) on coronal PET image quality. HighRes-HS PET images reconstructed from 5-min acquisitions are shown for a reference dataset without defects ($n = 0$), sparse DDB distributions with $n = 1$ – 128 affected blocks, and a clustered 16-DDB configuration corresponding to one detector electronics assembly (DEA). (a) Reconstructed PET images. (b) Relative-difference maps compared with the reference image. n = number of DDBs.

Lesion quantification in patient data demonstrated that the number and spatial configuration of DDBs affected quantitative accuracy, as shown in **Figure 26**. A single sparse DDB had minimal effect, with the most severe observed bias of -1.8% for SUV_{max} . With increasing numbers of sparse DDBs, quantitative accuracy decreased. SUV_{mean} remained relatively robust, with the most severe bias reaching -9.2% at 128 sparse DDBs and crossing the $\pm 5\%$ threshold at 32 DDBs. SUV_{max} was more sensitive. The most severe SUV_{max} bias increased from -1.8% for one DDB to 17.9% for 128 sparse DDBs and exceeded the $\pm 5\%$ threshold at 8 sparse DDBs. At 128 sparse DDBs, 92.0% of lesions still had SUV_{mean} within $\pm 5\%$, whereas 72.0% remained within this threshold for SUV_{max} . The spatial configuration of defects had a substantial effect on quantitative bias. With 16 sparse DDBs, the largest SUV_{mean} biases remained within $\pm 5\%$ under the investigated conditions, whereas a clustered 16-DDB defect increased SUV_{max} bias beyond 10%.

Clustering particularly affected SUV_{mean} , for which the most severe RD changed from 2.2% for sparse defects to -8.0% for clustered defects.

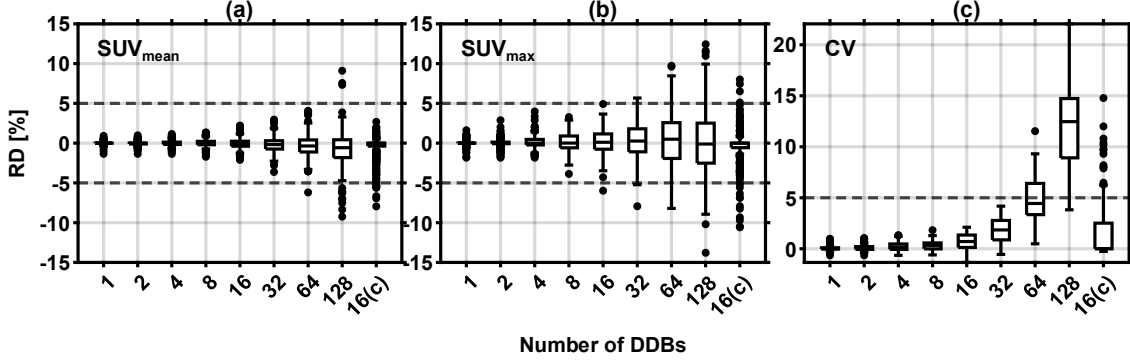


Figure 26 Lesion quantification in DDB-affected HighRes-HS reconstructions. Boxplots show relative difference (RD, %) in (a) SUV_{mean} , (b) SUV_{max} , and (c) coefficient of variation (CV) as a function of DDB number and spatial configuration for 5-min acquisitions. Boxes show the interquartile range, centre lines show medians, whiskers show $1.5 \times$ interquartile range, and points show individual lesion measurements. Dashed horizontal lines mark the $\pm 5\%$ RD threshold. The clustered 16-DDB scenario is labelled 16(c). DDB = defective detector block.

Reconstruction settings partially mitigated DDB-related errors. EARL2-compliant reconstruction reduced the most severe SUV_{max} bias at 32 sparse DDBs from -7.9% with HighRes-HS to -4.4% with the EARL2-compliant protocol in HS mode (EARL2-HS). EARL2-HS, however, was less effective for 16 clustered DDBs, with bias reductions ranging from 0.6% to 1.7% for SUV_{mean} and SUV_{max} , whereas the largest CV bias increased by an additional 10.2% relative error.

Switching from HS to UHS provided only marginal improvements in SUV metrics, reducing the most severe RDs by 1.1% for SUV_{mean} and 2.7% for SUV_{max} at 32 sparse DDBs with HighRes settings.

The greatest overall mitigation was obtained by combining UHS with EARL2-compliant reconstruction. At 32 sparse DDBs, the extreme SUV biases were reduced below the $\pm 5\%$ threshold. Nevertheless, 128 sparse DDBs and clustered 16-DDB defects still produced SUV biases of approximately 8–10%, indicating that reconstruction changes cannot fully

compensate for severe or spatially clustered detector-block loss.

Performance across the different reconstruction protocols, assessed using SUV_{mean} , SUV_{max} , and CV, is summarised in **Figure 27** and **Supplementary Figure 4**.

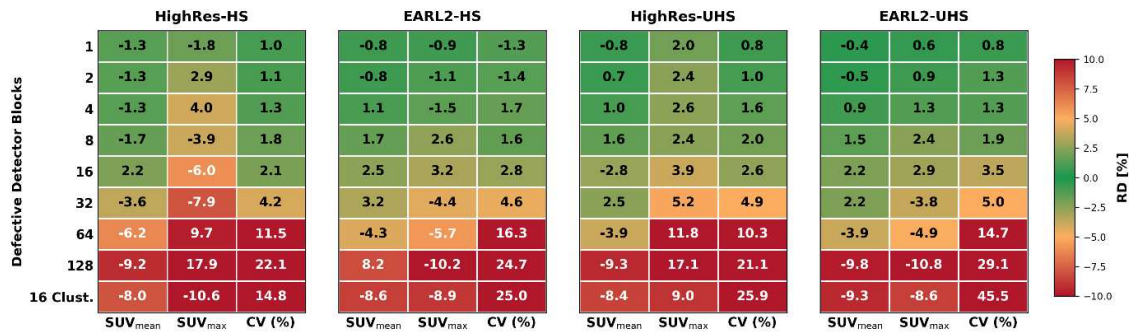


Figure 27 Most severe signed relative error induced by simulated defective detector blocks across reconstruction protocols. Heatmaps show the signed relative error (%) with the greatest magnitude for SUV_{mean} , SUV_{max} , and coefficient of variation (CV) across increasing numbers of defective detector blocks (DDBs) and the clustered 16-DDB scenario. Columns compare HighRes-HS, EARL2-HS, HighRes-UHS, and EARL2-UHS. HighRes = high-resolution reconstruction; EARL2 = EARL2-compliant reconstruction.

4.4.2 Simulated-Phantom Quantitative Analysis of DDB Configurations, Count Statistics, and Mitigation Strategies

The homogeneous cylindrical phantom clarified the physical and spatial dependence of DDB effects. Under standard count conditions (2.0 kBq/mL) with HighRes-HS reconstruction, one DDB induced a measurable local deviation of -5.0%. The effect increased for clustered defects. 8 clustered DDBs produced the most severe RD of -20.6%, whereas 8 sparsely distributed DDBs produced -7.0%. Increasing the clustered defect size beyond this range resulted in only negligible additional degradation, with -19.0% for a 16-DDB central cluster. Alternative arrangements of smaller clustered defects produced comparable deviations, with -16.4% for a 4-DDB line and -21.1% for a 4-DDB stack.

Count statistics influenced DDB-related bias. At 0.25 kBq/mL, a 16-DDB clustered defect

at the axial edge produced an RD of 143.4%, compared with 38.1% at 2.0 kBq/mL. Defects at axial positions with lower sensitivity produced larger deviations than centrally located defects. The volume affected by biases beyond $\pm 5\%$ increased with clustered defect size. At 2.0 kBq/mL and HighRes-HS, affected volumes increased from 1,501 mL for a 4-DDB stack to 5,084 mL for a 16-DDB cluster. Higher activity concentrations consistently reduced affected volumes, particularly for sparse defects. For 16 sparse DDBs, increasing activity from 0.25 to 2.0 kBq/mL reduced affected volumes from 10,599 mL to 298 mL.

Figure 28 [96] provides a comprehensive comparison of RDs and of the volumes affected when selected RD thresholds were exceeded across DDB numbers, spatial configurations, and activity concentrations.

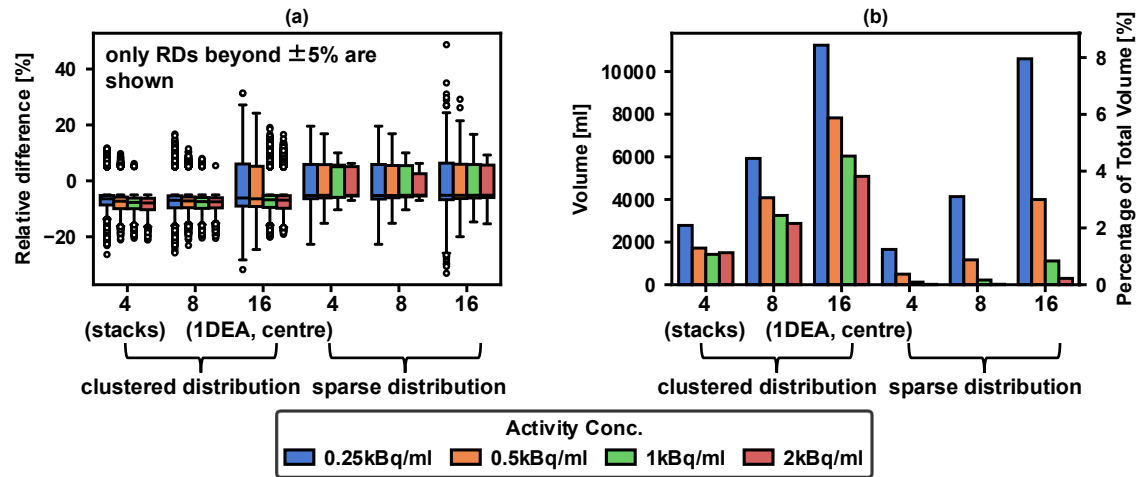


Figure 28 Activity-dependent impact of selected defective detector block (DDB) configurations in homogeneous phantom volume-of-interest analysis. (a) Boxplots show relative differences (RDs, %) for volumes of interest (VOIs) whose RDs exceeded the $\pm 5\%$ threshold under selected clustered and sparse DDB configurations at activity concentrations of 0.25, 0.5, 1.0, and 2.0 kBq/mL. (b) Corresponding affected volume in millilitres and as a percentage of the 133-L phantom volume. Analyses used HighRes-HS reconstruction. Boxes show the interquartile range, centre lines show medians, whiskers show $1.5 \times$ interquartile range, and points show individual VOIs. DEA = detector electronics assembly [96].

Figure 29(b),(c) [96] showed that clustered defects produced localised affected regions adjacent to the DDBs, marked in green. The affected regions expanded outward as the

cluster size increased, while the magnitude of bias decreased with distance from the defect. Analysis of the one-dimensional profiles along the oblique line (**Figure 29(d)**) [96] confirmed this spatial gradient. For instance, the VOI-based RD decreased from -21.1% near the defect to -2.0% on the opposite side of the phantom for a 4-DDB stack. In contrast, sparse DDBs resulted in a dispersed pattern of affected regions, characterised by fewer VOIs exceeding the $\pm 5\%$ threshold and a more homogeneous distribution across the phantom volume.

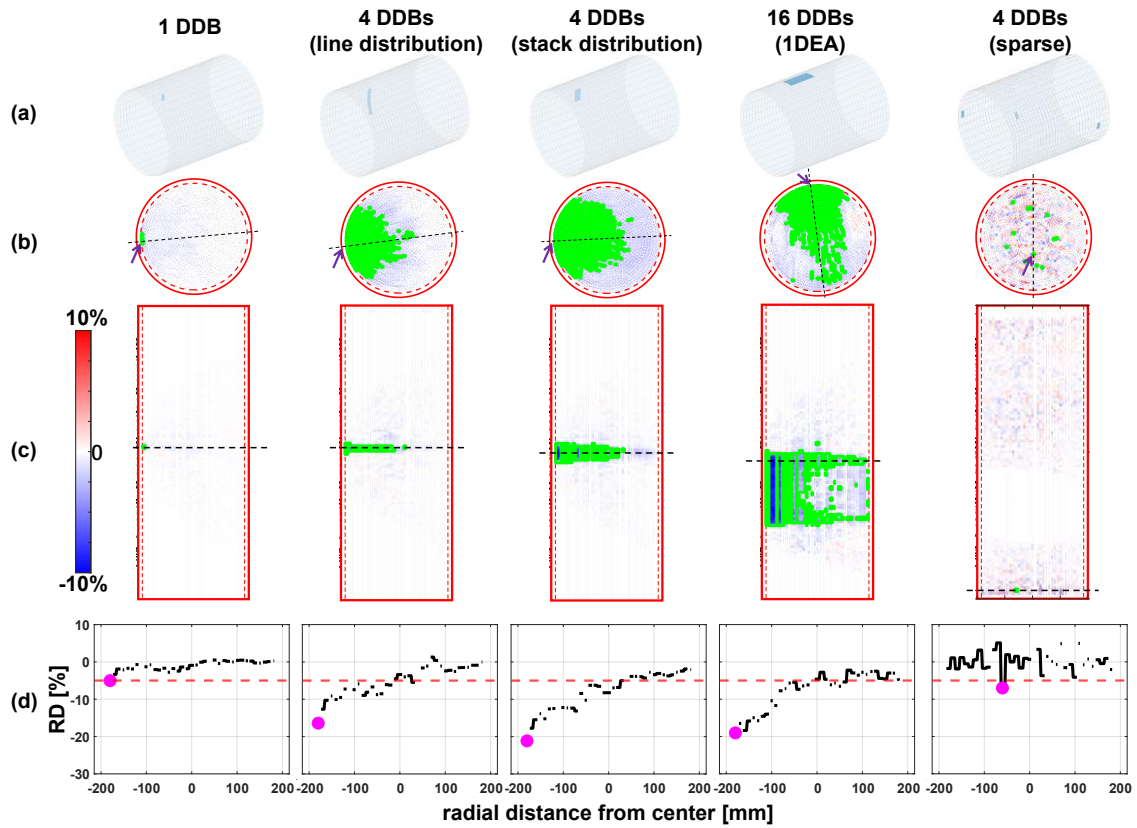


Figure 29 Spatial distribution of VOI-based relative differences caused by selected defective detector block configurations in the 40-cm cylindrical phantom at 2.0 kBq/mL. (a) Defective detector block (DDB) configurations: 1 DDB, 4 DDBs in a line, 4 DDBs in a stack, 16 DDBs corresponding to 1 detector electronics assembly (DEA), and 4 sparse DDBs. (b, c) Transaxial and oblique views of VOI (diameter $\varnothing = 10$ mm, length $L = 10$ mm); green overlays indicate VOIs with relative difference (RD) beyond $\pm 5\%$. Arrows mark the location of the most severe RD. (d) One-dimensional RD profiles along the oblique line; pink dots mark the most severe RD [96].

In phantom analyses, sensitivity mode and reconstruction protocol also modulated DDB-

related bias. For the 16-DDB central cluster at 2.0 kBq/mL with HighRes reconstruction, HS mode produced a slightly smaller bias than UHS mode (-19.0% versus -22.7%). EARL2-HS improved quantification robustness, especially under low-count conditions. For instance, the most severe deviation decreased from 143.4% with HighRes-HS to 75.7% with EARL2-HS for a 16-DDB edge cluster at 0.25 kBq/mL. The effect was smaller at 2.0 kBq/mL, decreasing from 38.1% to 27.1%. EARL2-compliant reconstruction also reduced affected volumes compared with HighRes. At 0.25 kBq/mL with 16 DDBs in HS mode, the EARL2-compliant protocol reduced the affected volume from 11,237 to 8,667 mL for a clustered central defect and from 10,599 to 5,607 mL for sparse defects.

Sensitivity mode showed pattern-dependent behaviour. For clustered defects, HS mode reduced affected volumes compared with UHS (e.g., from 4,006 to 2,875 mL for 8 DDBs at 2.0 kBq/mL, with the HighRes protocol). In contrast, for sparse defects under low-count conditions, HS mode increased the spatial extent of affected regions (e.g., from 7,958 to 10,599 mL for 16 sparse DDBs at 0.25 kBq/mL, with the HighRes protocol), consistent with the trend observed in patients.

5 Discussion

5.1 [^{18}F]FDG Parametric Imaging with an Abbreviated Dynamic Protocol as an Extension for Quantitative Imaging

The first methodological step of this thesis was to determine whether a long dynamic [^{18}F]FDG PET acquisition could be shortened to an acquisition window compatible with clinical LAFOV PET/CT workflows.

The results of previous work indicate that direct Patlak reconstruction using an sPBIF during the 45–65 min p.i. window provides the most reliable compromise between feasibility and quantitative fidelity among the investigated protocols. In this setting, sPBIF-based Ki and DV images showed close agreement with the patient-specific IDIF reference. Under the investigated 45–65 min p.i. protocol, the patient-specific sPBIF was sufficient for [^{18}F]FDG Ki estimation relative to the patient-specific IDIF reference [63,64].

The evaluation of HS and UHS modes in our study illustrates that a greater number of detected coincidence events is not the only determinant of an optimal clinical protocol. The two sensitivity modes produced highly consistent input functions and lesion-wise Patlak estimates. UHS mode showed slightly lower bias and improved precision for direct Patlak reconstruction, but at the cost of longer reconstruction times because of the larger number of LORs and the greater volume of event data. For instance, the end-to-end reconstruction duration ranged from 50 ± 3 min (HS) to 79 ± 3 min (UHS) using a dedicated workstation in the present study. This longer reconstruction time should be considered in high-throughput clinical schedules.

For sPBIF-based direct Patlak reconstruction, only negligible differences in Ki and DV estimates were observed among different numbers of Patlak frames (**Supplementary Table 1** [59]). A reconstruction based on four 5-min frames during 45–65 min p.i. provided sufficient temporal sampling for the Patlak fit while preserving event statistics

per frame [100]. Increasing the number of frames provides more regression points, but it also shortens the frame duration and increases noise in each dynamic frame [51]. The present data suggest that a Patlak framing configuration with four 5-min frames during 45–65 min p.i. provides adequate accuracy compared with the IDIF-based reference. More complex framing schemes offer no additional benefit for routine use.

In UHS mode, direct Patlak Ki increased TBR relative to SUV (17.2 ± 9.6 versus 6.2 ± 3.1), supporting its use when lesion contrast is the target. The TBR obtained with direct Patlak and sPBIF was not affected by the sensitivity mode. However, the TBR decreased as the scan duration was shortened. The values of 10.6 ± 5.4 (15 min) and 6.9 ± 3.5 (10 min) did not show significant improvement over the TBR obtained from SUV images.

Of note, a halo-shaped artefact around the bladder was clearly observed for the Ki estimate (45–65 min, $t^* = 45$ min) and less pronounced for the corresponding Ki estimate (50–65 min, $t^* = 50$ min) in **Figure 16(a)** [59].

This artefact likely reflects the non-linear Patlak plot in the bladder and the strong effect of t^* on bladder parametric estimates. The Patlak model, therefore, may not be suitable for bladder quantification [101]. Generally, the application of compartmental models to the bladder is challenging, as demonstrated by Wu et al. [102], who found one- and two-tissue irreversible and reversible compartmental models to be inapplicable.

Additionally, the present study employed a simplified compartmental model for the liver based on a single arterial input function. Given the dual blood supply of the liver from the hepatic artery and the portal vein, reversible compartmental models incorporating dual-input functions to provide a more accurate representation of hepatic tracer kinetics should be considered [103,104]. A more comprehensive lung model is warranted to account for the contributions of regional aeration, blood volume, and tissue water content to [^{18}F]FDG uptake [105].

Recently, several studies have investigated reduced acquisition times for parametric

values. van Sluis et al. reported that the dynamic examination could be shortened to 30 min (30–60 min p.i.) by sPBIF with bias of 7.4% in Ki estimate relative to IDIF-based reference (30–60 min p.i.) [106]. Another study by van Sluis et al. showed that the dynamic scan was further shortened to 10 min (55–65 min p.i.) using direct Patlak reconstruction with an sPBIF, but that the bias in lesion Ki estimates increased additionally 11% relative to the sPBIF-based estimates obtained from the 30–60 min p.i. [64]. However, in regions of the liver, spleen, and muscle, clear differences were observed between the sPBIF-based Ki estimates (55–65 min p.i.) and the 30-min sPBIF-based reference estimates [64]. Wu et al. reported that the sPBIF-based Ki estimates obtained using a 20-min dynamic scan (40–60 min p.i.) had diagnostic performance comparable to that of the IDIF-based estimates (20–60 min p.i.). When the dynamic scan was shortened to 16 min (44–60 min p.i.), the quality of the Ki images was significantly degraded, although all lesions could still be detected [107]. Wu et al. also pointed out that gross body motion during the examinations became a challenge to patient enrolment because it resulted in quantification artefacts, particularly with the 40-min dynamic protocol (20–60 min p.i.) [107]. Additionally, Viswanath et al. evaluated an alternative abbreviated scan protocol comprising two scans (0–15 min p.i. and 60–65 min p.i.), which yielded Ki estimates with the bias and precision of approximately 10% relative to the full-duration IDIF-based reference (0–65 min p.i.) [65]. However, this protocol may create organisational difficulties in high-throughput clinical practice because it requires 2 separate scans per patient.

In our larger NSCLC patient cohort, parametric values were not biased by the sensitivity modes (**Figure 18**). This finding may be attributed to the negligible differences between the corresponding input functions (RD between HS- and UHS-derived IDIFs: $-0.7 \pm 0.4\%$) and to the sufficient counting statistics provided by both modes. Thus, under the present acquisition and reconstruction conditions, the sensitivity-mode difference did not induce a substantial shift in the quantitative parametric estimates.

For NSCLC lesion subtypes, the findings showed that LUSC lesions had higher SUV and Ki than LUAD lesions, whereas DV did not differ substantially between histological subtypes. This pattern suggested that the higher [^{18}F]FDG uptake of squamous cell carcinomas is mainly driven by increased irreversible trapping or phosphorylation-related glucose metabolism, rather than by differences in reversible distribution or vascular contribution. This interpretation was consistent with the established hypermetabolic phenotype of LUSC and with prior static [^{18}F]FDG PET studies on histological subtype differentiation [21]. Importantly, the parametric data provided a mechanistic explanation for the SUV difference that Ki confirmed that the subtype-related uptake difference was linked to the trapping component of [^{18}F]FDG kinetics.

For PD-L1 status, PD-L1-positive lesions showed higher Ki and DV than PD-L1-negative lesions, whereas the between-group difference in SUV narrowly failed to meet the conventional threshold for statistical significance ($p = 0.051$). This distinction is important because the value of parametric imaging extends beyond maximising classification performance. It also enables the separation of kinetic components that are otherwise integrated within a single SUV measurement. Nevertheless, in the present cohort, the parametric metrics did not clearly improve the discrimination of PD-L1 status relative to SUV, suggesting substantial overlap in the PD-L1-related information captured by static and parametric measures. This finding is consistent with previous work demonstrating an association between [^{18}F]FDG uptake and PD-L1 expression in NSCLC [108].

5.2 Motion Correction as a Prerequisite for Quantitative Accuracy

After establishing that abbreviated parametric imaging is feasible and clinically applicable, the next question is whether the resulting quantitative information can remain accurate in the presence of patient motion. This issue affects both parametric-imaging accuracy [37,109] and routine static PET quantification [110]. However, the performance of respiratory motion-correction methods is typically assessed by comparison with

uncorrected or gated PET images because a patient-specific motion-free reference is inherently unavailable in vivo [70,111,112].

The clinical analysis confirmed that respiratory motion correction increased SUV, improved lesion conspicuity and reduced motion blurring, consistent with previous studies [34,113,114]. For instance, Dias et al reported an overall 14 % increase in the measured median SUV_{max} after motion correction [34]. Büther et al presented that SUV_{mean} of 31 liver lesions increased from 9.0 ± 3.8 (uncorrected) to 13.7 ± 11.4 using data-driven motion correction, and the corresponding lesion volumes decreased from $0.5 \pm 2.4 \text{ cm}^3$ (uncorrected) to $0.3 \pm 1.3 \text{ cm}^3$ after motion correction [113]. Using the corresponding motion-free reference, the present study found that the correction strategy producing the largest apparent SUV recovery was not consistently the most accurate. Instead, quantitative performance depended on both lesion location and the parameter being evaluated. Therefore, the objective of respiratory motion correction should not be to maximise SUV recovery itself, but to recover the underlying tracer distribution as accurately as possible.

The two investigated motion-correction strategies illustrated this observation. The data-driven approach consistently produced larger SUV increases and stronger MTV reductions in both patients and simulations. However, comparison with the motion-free reference showed that this apparent advantage was confined primarily to lesions adjacent to the diaphragm, whereas the image-based approach remained closer to the reference for several pulmonary lesions despite producing smaller correction-induced changes. These findings indicate that different correction strategies exhibited different quantitative performance characteristics depending on lesion location rather than indicating that one approach was universally superior.

As expected, lesions adjacent to the diaphragm exhibited the largest motion-induced quantitative errors, whereas lesions further away were considerably less affected [34,110]. Additional simulations demonstrated progressively increasing SUV overestimation for

the data-driven approach towards the lung apex, whereas this effect became less pronounced for larger lesions (**Supplementary Figure 2**). Together, these observations indicate that correction performance varies systematically with lesion location and lesion size.

The present study also demonstrates how the simulation framework can be combined with an anatomically realistic patient model and the clinical reconstruction pipeline. Similar scanner-specific PET simulation frameworks have been reported previously [115–117]. This provides an objective framework for evaluating and comparing respiratory motion-correction algorithms under controlled conditions that closely reflect clinical practice. This benchmarking cannot be achieved in patient studies alone. The same methodology can readily be transferred to other PET systems, provided similarly well-validated scanner models are available.

Despite the short duration of static LAFOV PET acquisitions, respiratory motion management remains necessary for accurate quantification in the thorax and upper abdomen. Gross body motion represents an additional major source of motion-related error, particularly in parametric imaging based on dynamic acquisitions, for which the longer examination duration increases the likelihood of patient displacement. Guo et al. [118] and Merlin et al. [119] implemented motion-correction methods for Patlak graphical analysis on SAFOV PET systems. However, motion correction integrated with direct Patlak reconstruction has not yet been established for LAFOV PET systems and therefore represents an important direction for future research. Robust, anatomically tailored correction of both respiratory and gross body motion is consequently required for static and dynamic acquisitions and is essential for achieving accurate and reliable quantitative PET imaging.

5.3 System Robustness and Reliability as a Necessity for Quantitative Accuracy

The final component of the thesis addressed the robustness of an LAFOV PET scanner,

which is an important requirement for quantitative imaging. The investigation of the effects of DDBs provided an operational boundary for applying the quantitative methods developed in the earlier parts of the thesis.

According to the patient analysis, up to 16 sparsely distributed DDBs resulted in maximum SUV biases of approximately 6%. In contrast, the same DDB pattern yielded biases of up to 15% in phantom simulations at 2.0 kBq/mL. Visual assessment (**Figure 29** [96]) revealed that the larger deviations occurred at the surface of the phantom and in proximity to the defect locations. Similar spatial patterns were observed in the patient data (**Figure 25**), with SUV biases exceeding $\pm 10\%$ in peripheral regions such as the shoulder. However, only a limited number of lesions were located at these large radial distances (**Figure 13**), constraining the ability of the patient-based analysis to capture these extreme deviations. Consistent with the patient observations, phantom results showed that the affected volume above the $\pm 5\%$ threshold decreased from 300 mL for 16 sparse DDBs to 20 mL for 8 sparse DDBs. Based on the combined findings, a tolerance of up to 8 sparsely distributed DDBs (equivalent to 64 mini blocks) maintained stable quantification performance under the investigated conditions.

Beyond the number of defects, spatial distribution had a critical impact on quantification performance. Clusters of adjacent DDBs introduced biases two to four times as large as those produced by their sparsely distributed counterparts in both lesion and phantom evaluations. The geometric shape and the position of the clustered DDBs also modulated this impact. In general, sparse defects induce a diffuse bias that can be compensated for by the high-sensitivity system. Conversely, clustered defects concentrate missing LORs within a confined region, possibly impeding the reconstruction algorithm's ability to handle missing data. These findings align with conventional SAFOV studies by Buchert et al. [44] and Elhami et al. [45]. In practice, DDBs fail stochastically, and the probability of adjacent blocks failing simultaneously and forming a cluster is low (**Supplementary Table 3**), particularly for 8 or 16 DDBs. Despite their rarity, scanner operation with up to

4 adjacent DDBs (equivalent to 32 mini blocks) would be expected to have minimal influence on PET quantification.

The DDB-induced biases also demonstrate that quantitative robustness depends on the metric and reconstruction protocol. SUV_{max} was the most defect-sensitive metric, consistent with its dependence on a single voxel. This single-voxel dependence makes SUV_{max} highly sensitive to image noise and local count fluctuations [120,121].

Reconstruction settings had a notable influence on DDB-induced biases. EARL2-compliant reconstructions, using larger voxels and post-filtering, reduced biases across all metrics. In both patient and phantom studies, this reduction was sufficient to maintain acceptable quantification performance even at 32 sparse DDBs. A more moderate improvement was obtained by using UHS rather than HS (**Figure 27**). The combination of EARL2-compliant reconstructions with UHS mode yielded the most robust PET quantification in both patient and phantom studies.

The magnitude of DDB-induced quantification biases was modulated by count statistics. In the phantom study, lower activity concentrations resulted in substantially larger biases and affected volumes (**Figure 28** [96]). Activity concentrations of 0.25–2.0 kBq/mL were simulated in the phantom, while the patient data, with an average lesion uptake of 18.2 kBq/mL, did not allow assessment under low-activity conditions. For comparison, an additional phantom simulation was performed (**Supplementary Figure 5** [96]), which yielded biases at activity concentrations similar to those observed in patients. These findings support the observation that lower count statistics amplify DDB-related quantification errors.

The DDB analysis simulated detector-block defects by removing listmode events associated with predefined detector blocks. This approach isolates the effect of complete block loss and enables controlled comparisons, but it cannot reproduce all forms of real hardware degradation. In clinical systems, partial degradation in timing resolution, energy estimation, crystal identification, or shared electronics may affect neighbouring blocks

without producing a complete block failure [122].

From an operational perspective, these findings support a more evidence-based approach to LAFOV PET quality control. With HighRes reconstruction protocol, the results suggest that the Biograph Vision Quadra can tolerate up to 8 sparse DDBs (equivalent to 64 mini blocks) or up to 4 clustered DDBs (equivalent to 32 mini blocks) without immediate loss of clinically relevant quantitative accuracy. With the EARL2-compliant reconstruction protocol, the scanner can suffer up to 32 sparse DDBs (equivalent to 256 mini blocks). By comparison, current quality control protocols and vendor guidelines set a highly conservative threshold of 10 mini blocks and are derived primarily from SAFOV PET systems.

When DDBs detected during quality control result in the scanner being taken out of service, recalibration and a complete system reset, referred to as a “full setup”, must be performed using a uniform cylindrical ^{68}Ge phantom [40]. On average, these procedures require approximately 3.5 hours, although the exact duration depends on the activity of the ^{68}Ge phantom. The findings could therefore support higher thresholds for DDBs, thereby reducing unnecessary downtime and preserving scanner availability.

Although the quantitative effects of DDBs with normalisation-based compensation have been investigated, the specific contribution of a mismatch between the detector status during patient acquisition and that represented by the normalisation profile has not been systematically evaluated, particularly when DDBs remain undetected during daily quality control.

5.4 Conclusion

This thesis demonstrates that the technical advantages of LAFOV PET/CT can be translated into enhanced clinical quantitative imaging when clinical feasibility, quantitative accuracy, and system robustness are addressed together. Rather than evaluating LAFOV PET/CT as a technical upgrade alone, this thesis defines a

translational pathway in which parametric imaging protocols become clinically practicable, correction methods are validated against appropriate references, and scanner performance remains reliable under realistic operational conditions.

The abbreviated [^{18}F]FDG direct Patlak protocol established the feasibility component of this pathway. Instead of a typically hour-long acquisition, a 20-min acquisition using a patient-specific sPBIF enabled parametric imaging and maintained close agreement with patient-specific IDIF references. The subsequent application in treatment-naïve NSCLC patients showed that kinetic parameters provide information related to tumour subtype and PD-L1 status, while remaining complementary to conventional SUV-based assessment. LAFOV PET/CT enables [^{18}F]FDG parametric imaging to move from a technically demanding research protocol toward a clinically practicable extension of standard PET/CT.

The motion-correction and detector-defect studies defined the conditions under which such quantitative imaging can remain accurate and robust. The motion-correction work showed that respiratory motion substantially affects lesion uptake, MTV, and morphology, particularly in thoracic and upper-abdominal regions. Visual recovery after correction is not sufficient evidence of quantitative accuracy. The combined patient and simulation framework, incorporating a motion-free reference, may support the future development and objective evaluation of respiratory motion-correction algorithms. The DDB analysis further showed that LAFOV PET/CT is relatively tolerant of up to 8 sparse or 4 clustered DDBs.

Together, these findings support LAFOV PET/CT as an accurate quantitative imaging platform when appropriate acquisition, correction, and quality-control strategies are integrated.

Summary

Long axial field of view (LAFOV) PET/CT provides markedly increased sensitivity and an extended axial field of view. The central research question of this thesis was whether these physical advantages could be translated into the enhancement of clinical quantitative imaging. This question was addressed through three interrelated study components: [^{18}F]FDG parametric imaging using an abbreviated dynamic scan and clinical exploration of this approach in non-small cell lung cancer (NSCLC); quantification of respiratory motion correction using patient cohorts and a motion-free reference; and assessment of robustness against defective detector blocks (DDBs). All investigations were performed using the Biograph Vision Quadra LAFOV PET/CT. First, abbreviated dynamic [^{18}F]FDG protocols were optimised for direct Patlak reconstruction using patient-specific image-derived input functions (IDIFs) and scaled population-based input functions (sPBIFs) in high-sensitivity (HS) and ultra-high-sensitivity (UHS) modes. The optimised protocol was applied to treatment-naïve patients with histopathologically confirmed NSCLC to analyse standardised uptake value (SUV), net influx rate constant (K_i), and distribution volume (DV) in relation to tumour subtype and programmed death-ligand 1 (PD-L1) status. Respiratory motion correction methods were then evaluated using clinical datasets and a four-dimensional extended cardiac-torso (XCAT) phantom simulated with a validated digital twin of the Biograph Vision Quadra, thereby providing a motion-free reference. Finally, DDBs were simulated in patient and phantom datasets to assess the influence of the number and spatial distribution of DDBs, count statistics, sensitivity mode, and reconstruction protocol on SUV_{mean} , SUV_{max} , and image noise.

The protocol-optimisation study showed that a 20-min acquisition (45–65 min p.i.), reconstructed with four Patlak frames and patient-specific sPBIFs, provided a reliable balance between clinical feasibility and quantitative fidelity under the investigated conditions. This protocol preserved K_i estimates relative to patient-specific IDIF-based references and produced higher tumour-to-background contrast than conventional SUV

images. Shorter acquisition windows increased deviations and reduced image fidelity. In the NSCLC cohort, lung squamous cell carcinoma lesions showed higher SUV_{max} and Ki_{max} than lung adenocarcinoma lesions, whereas DV_{max} did not differ significantly between histological subtypes. PD-L1-positive lesions showed higher Ki_{max} and DV_{max} than PD-L1-negative lesions, whereas SUV_{max} showed only a non-significant trend. Thus, Ki and DV should be reported as complementary metrics alongside SUV .

The motion-correction study demonstrated that quantitative accuracy also requires spatial fidelity. Respiratory motion caused lesion blurring, uptake underestimation, and lesion volume overestimation, particularly near the diaphragm. Two correction methods were evaluated, and both improved visual lesion delineation. However, comparison with the motion-free reference showed that greater sharpening and larger SUV recovery did not necessarily correspond to more accurate recovery. The data-driven method produced greater uptake recovery and a more compact lesion appearance but tended to overcorrect selected pulmonary lesions. The image-based method was more conservative relative to the motion-free reference, although it introduced greater image noise. Therefore, motion correction should be evaluated according to lesion location and the quantitative metric being assessed.

The detector-block defect analysis showed that DDBs induced quantitative bias, with the magnitude of bias depending on the number, location, and distribution of DDBs, as well as the count statistics of the examination. The Biograph Vision Quadra maintained quantitative reliability with up to eight sparse or four clustered DDBs under the investigated conditions. EARL2-compliant reconstruction in UHS mode partially mitigated deviations but could not fully compensate for severe detector-block defects.

In conclusion, this thesis shows that the technical advantages of LAFOV PET can be translated into accurate and reliable quantitative imaging when combined with appropriate acquisition protocols, motion-correction strategies, and quality-control procedures.

Zusammenfassung

Long axial field of view (LAFOV) PET/CT Scanner haben ein erweitertes axiales Gesichtsfeld und eine deutlich höhere Sensitivität. Die zentrale Forschungsfrage dieser Dissertation war, ob diese physikalischen Vorteile in eine Verbesserung der klinischen quantitativen Bildgebung übertragen werden können. Diese Fragestellung wurde anhand von drei miteinander verknüpften Studienkomponenten untersucht: der [^{18}F]FDG-parametrischen Bildgebung unter Verwendung eines verkürzten dynamischen Scans sowie der klinischen Erprobung dieses Ansatzes beim nicht-kleinzelligen Lungenkarzinom (NSCLC); der Quantifizierung der Atembewegungskorrektur anhand von Patientenkohorten und einer bewegungsfreien simulierten Phantom Referenz; sowie der Bewertung der Robustheit gegenüber defekten Detektorblöcken (defective detector blocks, DDBs). Alle Untersuchungen wurden mit dem Biograph Vision Quadra LAFOV PET/CT durchgeführt.

Zunächst wurden verkürzte dynamische [^{18}F]FDG-Protokolle für die direkte Patlak-Rekonstruktion optimiert. Dabei wurden patientenspezifische bildbasierte Input-Funktionen (image-derived input functions, IDIFs) und skalierte populationsbasierte Input-Funktionen (scaled population-based input functions, sPBIFs) im High-Sensitivity (HS) und Ultra-High-Sensitivity (UHS) Modus verwendet. Das optimierte Protokoll wurde bei therapienaiven Patienten mit histopathologisch bestätigtem NSCLC angewendet, um den standardisierten Uptake-Wert (SUV), die Netto-Influxratenkonstante (K_i) und das Verteilungsvolumen (DV) in Bezug auf Tumorsubtyp und Programmed-Death-Ligand-1 (PD-L1) Status zu analysieren. Anschließend wurden Methoden zur Atembewegungskorrektur anhand klinischer Datensätze und eines 4D Extended-Cardiac-Torso (XCAT) Phantoms evaluiert, das mit einem validierten digitalen Zwilling des Quadra simuliert wurde und somit eine bewegungsfreie Referenz ermöglichte. Abschließend wurden DDBs in Patienten- und Phantomdatensätzen simuliert, um den Einfluss der Anzahl und räumlichen Verteilung der DDBs, der

Zählstatistik, des Sensitivitätsmodus und des Rekonstruktionsprotokolls auf SUV_{mean} , SUV_{max} und das Bildrauschen zu untersuchen.

Die Studie zur Protokolloptimierung zeigte, dass eine 20-minütige Akquisition von 45–65 min p.i., rekonstruiert mit vier Patlak-Frames und patientenspezifischen sPBIFs, unter den untersuchten Bedingungen ein zuverlässiges Gleichgewicht zwischen klinischer Durchführbarkeit und quantitativer Genauigkeit bot. Dieses Protokoll bewahrte die Ki Bestimmung im Vergleich zu patientenspezifischen IDIF-basierten Referenzen und führte zu einem höheren Tumor-zu-Hintergrund Kontrast als konventionelle SUV Bilder. Kürzere Akquisitionszeiten erhöhten die Abweichungen. In der NSCLC-Kohorte zeigten Läsionen des Plattenepithelkarzinoms der Lunge höhere SUV_{max} und Ki_{max} Werte als Läsionen des Adenokarzinoms der Lunge, während sich DV_{max} zwischen den histologischen Subtypen nicht signifikant unterschied. PD-L1-positive Läsionen zeigten höhere Ki_{max} und DV_{max} Werte als PD-L1 negative Läsionen, während SUV_{max} lediglich einen nicht signifikanten Trend zeigte. Daher sollten Ki und DV als ergänzende Messgrößen zusätzlich zum SUV berichtet werden.

Die Studie zur Bewegungskorrektur zeigte, dass quantitative Genauigkeit auch räumliche Genauigkeit erfordert. Atembewegung führte zu Läsionsunschärfe, Unterschätzung der Traceraufnahme und Überschätzung des Läsionsvolumens, insbesondere in der Nähe des Zwerchfells. Zwei Korrekturmethoden wurden evaluiert, und beide verbesserten die visuelle Abgrenzung der Läsionen. Der Vergleich mit der bewegungsfreien Referenz zeigte jedoch, dass eine stärkere Schärfung der Läsionsgrenzen und eine höhere SUV Werte nicht zwangsläufig einer genaueren Wiederherstellung der bewegungsfreien Referenz entsprachen. Die datengesteuerte Methode führte zu einer stärkeren Wiederherstellung der Aufnahme und zu einem kompakteren Erscheinungsbild der Läsionen, neigte jedoch bei ausgewählten pulmonalen Läsionen zu einer Überkorrektur. Die bildbasierte Methode war im Vergleich zur bewegungsfreien Referenz konservativer, ging jedoch mit einer stärkeren Zunahme des Bildrauschens einher. Daher sollte die

Bewegungskorrektur in Abhängigkeit von der Läsionslokalisation und der jeweiligen quantitativen Messgröße bewertet werden.

Die Analyse der Detektorblockdefekte zeigte, dass DDBs quantitative Verzerrungen verursachen, deren Ausmaß von der Anzahl, Lokalisation und Verteilung der DDBs sowie von der Zählstatistik der Untersuchung abhängt. Unter den untersuchten Bedingungen blieb die quantitative Zuverlässigkeit des Siemens Biograph Quadra bei bis zu acht verstreuten oder vier gruppierten DDBs erhalten. Eine EARL2-konforme Rekonstruktion im UHS-Modus konnte Abweichungen teilweise reduzieren, jedoch schwere Detektorblockdefekte nicht vollständig kompensieren.

Zusammenfassend zeigt diese Dissertation, dass die technischen Vorteile der LAFOV-PET in eine genaue und zuverlässige quantitative Bildgebung übertragen werden können, sofern sie mit geeigneten Akquisitionsprotokollen, Strategien zur Bewegungskorrektur und Qualitätskontrollverfahren kombiniert werden.

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Supplementary Materials

Supplementary Table 1 Bias and precision of Ki and DV estimates from sPBIF-based direct Patlak reconstruction. Results are shown for high sensitivity (HS) and ultra-high sensitivity (UHS) modes, Patlak start times $t^* = 45, 50,$ and 55 min, and 4–6 Patlak frames. Values are reported as mean bias $\pm$ precision in percent relative to the IDIF-based method reconstructed with the same settings. Ki = net influx rate constant; DV = distribution volume [59].

t^*	number of Patlak frames	sensitivity mode	bias $\pm$ precision (Ki)	bias $\pm$ precision (DV)
45 min	4	HS	$2.4 \pm 3.0\%$	$20.2 \pm 9.9\%$
		UHS	$2.7 \pm 3.4\%$	$18.1 \pm 7.5\%$
	5	HS	$2.2 \pm 3.6\%$	$19.4 \pm 9.0\%$
		UHS	$1.6 \pm 3.9\%$	$20.2 \pm 8.8\%$
	6	HS	$2.5 \pm 3.2\%$	$20.4 \pm 10.7\%$
		UHS	$2.1 \pm 3.6\%$	$19.9 \pm 8.4\%$
50 min	4	HS	$13.0 \pm 9.5\%$	$6.5 \pm 17.4\%$
		UHS	$15.0 \pm 10.5\%$	$2.6 \pm 13.9\%$
	5	HS	$12.3 \pm 8.6\%$	$7.8 \pm 17.3\%$
		UHS	$14.0 \pm 9.3\%$	$4.3 \pm 14.9\%$
	6	HS	$12.5 \pm 8.6\%$	$8.1 \pm 19.9\%$
		UHS	$14.3 \pm 9.2\%$	$3.9 \pm 15.0\%$
55 min	4	HS	$32.6 \pm 19.0\%$	$-25.2 \pm 26.6\%$
		UHS	$34.5 \pm 22.5\%$	$-29.2 \pm 17.3\%$
	5	HS	$31.1 \pm 17.8\%$	$-22.2 \pm 30.6\%$
		UHS	$33.2 \pm 21.4\%$	$-26.8 \pm 18.9\%$
	6	HS	$31.4 \pm 18.2\%$	$-23.5 \pm 26.2\%$
		UHS	$33.4 \pm 21.7\%$	$-27.4 \pm 17.9\%$

Supplementary Table 2 Patient-level and phantom regional relative-difference statistics after respiratory motion correction. Relative differences are reported for data-driven and image-based motion correction compared with the corresponding uncorrected datasets for patient and phantom analyses. p-values compare data-driven and image-based motion-correction methods within each structure. MTV = metabolic tumour volume; MoCo = motion correction.

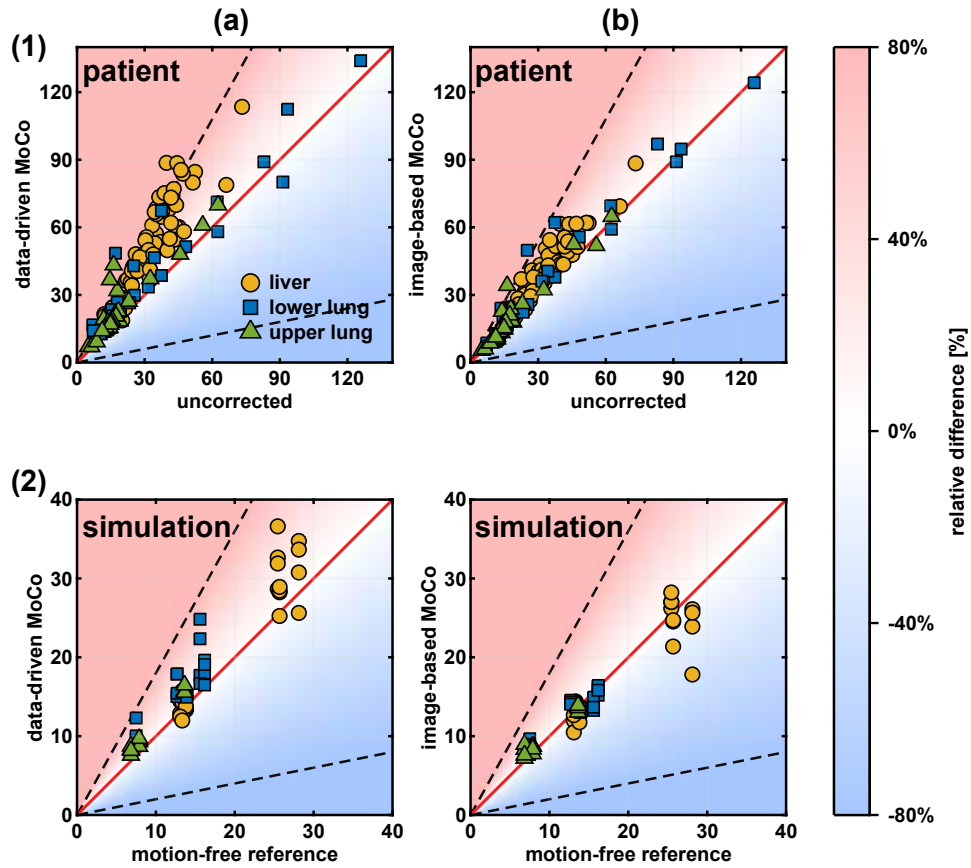
parameter	structure	data-driven MoCo (%)	image-based MoCo (%)	p-value
SUV _{mean} (patient)	liver	48.1 ± 18.9	17.0 ± 12.0	<0.01
	lower lung	32.5 ± 21.2	16.3 ± 15.6	0.06
	upper lung	28.4 ± 32.0	10.4 ± 17.2	<0.01
SUV _{max} (patient)	liver	47.0 ± 17.9	15.7 ± 11.5	<0.01
	lower lung	31.8 ± 20.4	14.4 ± 14.8	0.01
	upper lung	28.9 ± 31.8	9.9 ± 17.3	<0.01
MTV (patient)	liver	-52.5 ± 14.8	-11.1 ± 20.6	<0.01
	lower lung	-29.6 ± 15.7	-3.8 ± 17.9	<0.01
	upper lung	-26.6 ± 17.0	-4.6 ± 19.0	<0.01
SUV _{mean} (phantom)	liver	55.3 ± 16.1	34.5 ± 11.7	0.01
	lower lung	45.1 ± 29.3	18.0 ± 11.3	0.06
	upper lung	17.5 ± 6.5	5.6 ± 4.3	0.06
SUV _{max} (phantom)	liver	52.7 ± 16.5	34.8 ± 14.5	0.02
	lower lung	43.5 ± 27.6	18.0 ± 12.8	0.06
	upper lung	21.3 ± 4.8	10.6 ± 6.4	0.12
MTV (phantom)	liver	-46.5 ± 15.4	-23.5 ± 22.6	<0.01
	lower lung	-33.4 ± 16.1	-4.6 ± 15.9	0.02
	upper lung	-22.0 ± 7.7	-21.9 ± 20.7	0.09

Supplementary Table 3 Probability of adjacent DDB cluster formation in stochastic sparse-defect simulations. The table reports the probability (%) of obtaining at least one adjacent DDB cluster of each size when 8, 16, 32, 64, or 128 sparse DDBs were simulated randomly in a PET system with 1,216 detector blocks. Values are based on 10,000 simulations. * indicates probability < 0.01%. DDB = defective detector block.

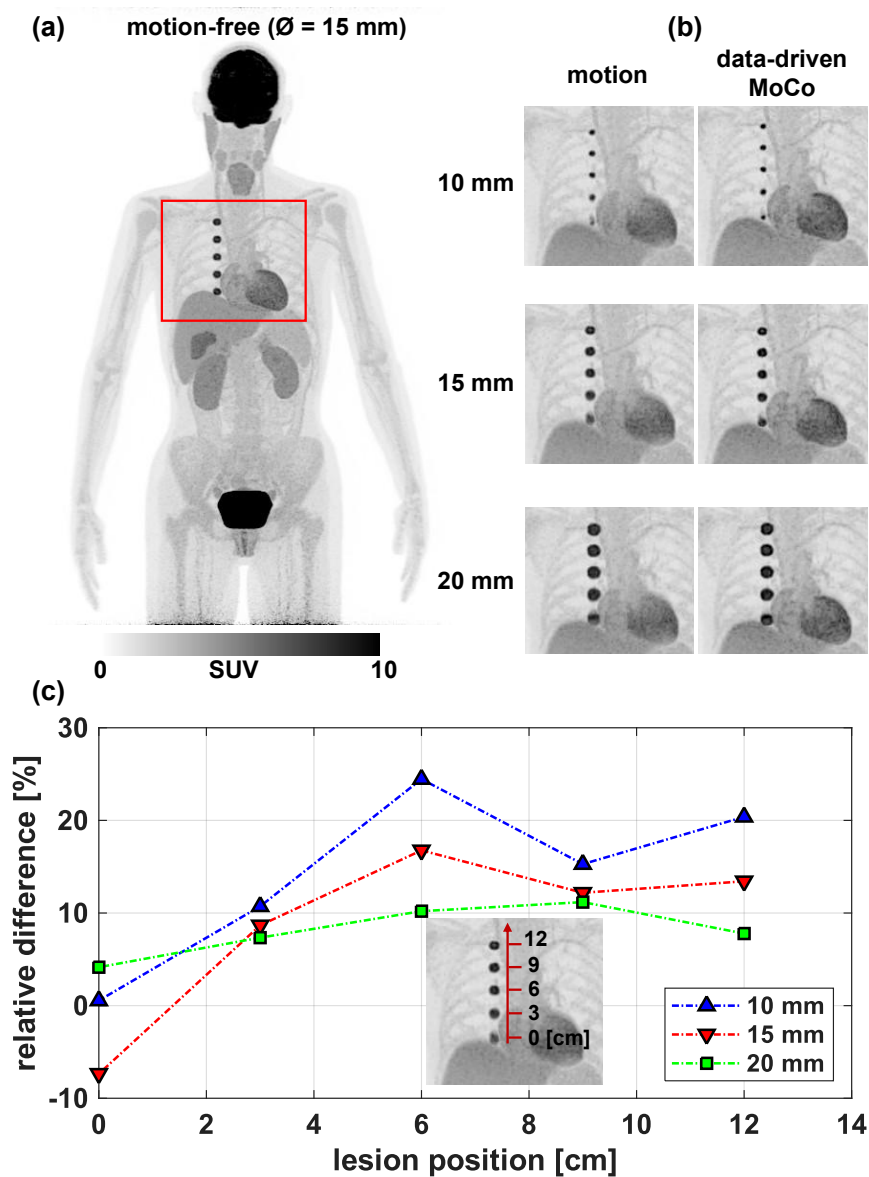
sparse DDBs (#)	size of adjacent DDBs cluster											
	1	2	3	4	5	6	7	8	9	10	11	12
8	100	8.34	0.15	*	*	*	*	*	*	*	*	*
16	100	31.1	1.25	0.05	*	*	*	*	*	*	*	*
32	100	77.6	8.6	0.78	0.06	0.02	*	*	*	*	*	*
64	100	99.4	49.8	8.59	1.52	0.22	0.05	0.02	0.01	*	*	*
128	100	100	98.0	65.3	24.6	8.13	2.68	0.90	0.33	0.09	0.04	0.02

*: Probability < 0.01%

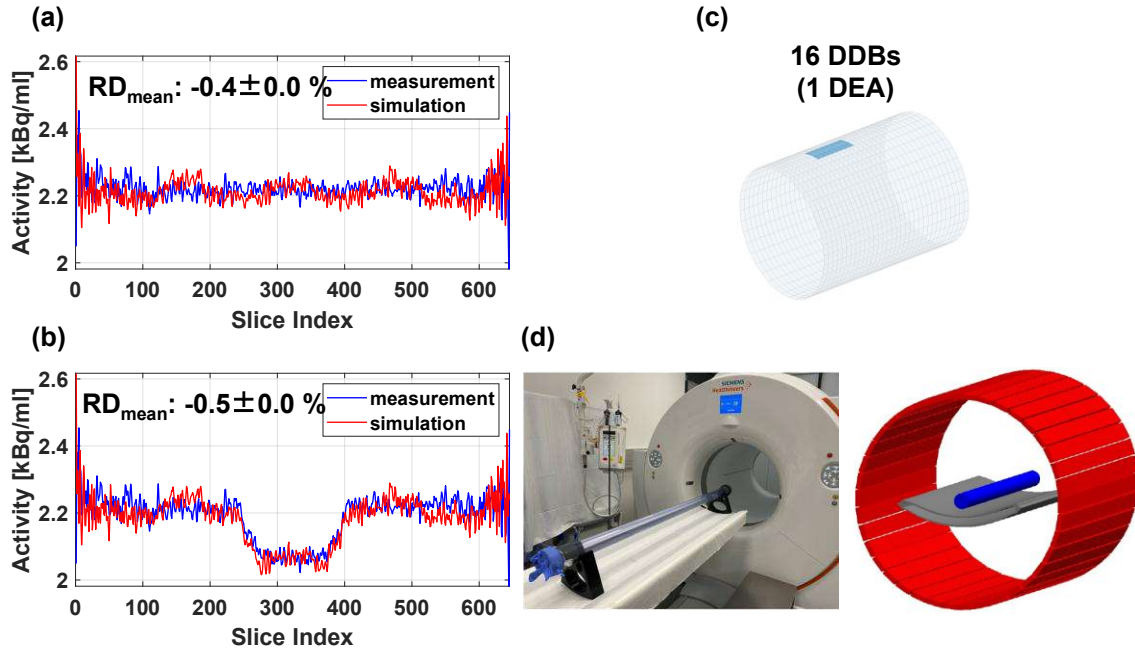
Defective detector blocks (DDBs) were assumed to occur stochastically within the PET gantry. Because neighbouring defective blocks may occur by chance and form spatial clusters, the probability of cluster formation is expected to increase with the total number of DDBs. To estimate this probability for the investigated LAFOV PET system comprising 1,216 detector blocks, we simulated 10,000 random DDB patterns containing 8, 16, 32, 64, or 128 DDBs. For each simulated pattern, the occurrence of adjacent DDB clusters of varying sizes was quantified. Simulations were performed using MATLAB R2026a (MathWorks, Natick, MA, USA).



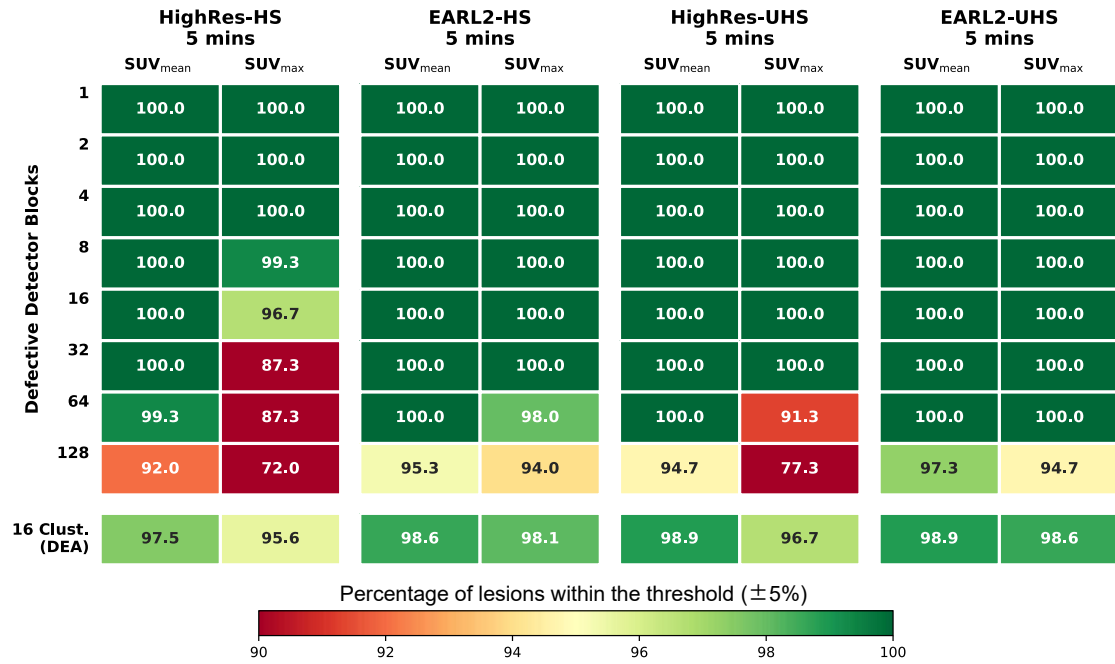
Supplementary Figure 1 Lesion SUV_{max} changes after respiratory motion correction in patient and simulated phantom datasets. Row 1 compares data-driven and image-based motion-corrected lesion values from patient datasets with corresponding uncorrected values. Row 2 compares phantom motion-corrected values with the motion-free reference. Dashed lines indicate $\pm 80\%$ relative difference. Circles, squares, and triangles denote liver, lower-lung, and upper-lung lesions, respectively. MoCo = motion correction.



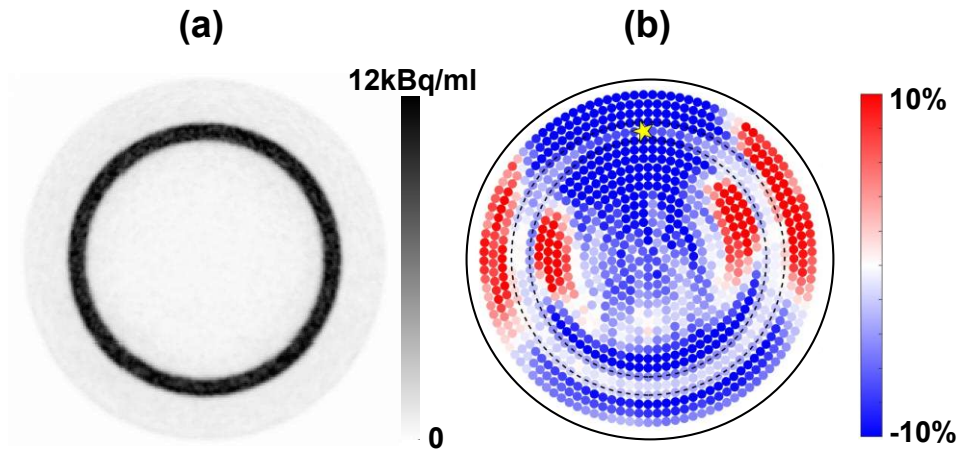
Supplementary Figure 2 Influence of lesion location and lesion size on SUV_{mean} recovery after data-driven respiratory motion correction. (a) Maximum-intensity projection of the motion-free reference phantom containing 5 uniformly spaced 15-mm lung lesions; the red box marks the region enlarged in panel b. (b) Enlarged maximum-intensity projections of 10-, 15-, and 20-mm lesions under respiratory motion with 2-cm maximum amplitude and after data-driven motion correction. (c) Relative difference in SUV_{mean} between data-driven motion-corrected images and the motion-free reference for 5 lesion positions. MoCo = motion correction.



Supplementary Figure 3 Validation of simulated axial activity-concentration profiles against physical measurements using a cylindrical phantom (diameter, 5.5 cm; length, 140 cm). For each axial slice, the mean activity concentration within a 37-mm-diameter cylindrical region of interest was compared between measurement and simulation under (a) reference conditions and (b) a clustered configuration of 16 defective detector blocks (DDBs) associated with one central detector electronics assembly (DEA). The mean relative differences (RD_{mean}) between simulation and measurement were $-0.4 \pm 0.0\%$ and $-0.5 \pm 0.0\%$ for the reference and 16-DDB configurations, respectively. (c) Schematic representation of the clustered 16-DDB configuration. (d) Photograph of the cylindrical phantom positioned in the LAFOV PET/CT scanner and the corresponding phantom representation within the digital twin of the LAFOV PET scanner geometry [96].



Supplementary Figure 4 Lesion-based robustness across defective detector block (DDB) configurations and reconstruction protocols. Split-cell heatmaps show the percentage of lesions with relative difference (RD) within the predefined $\pm 5\%$ threshold for SUV_{mean} and SUV_{max} across increasing numbers of DDBs and the clustered 16-DDB scenario. Reconstruction protocols are HighRes-HS, EARL2-HS, HighRes-UHS, and EARL2-UHS for 5-min acquisitions. HighRes = high-resolution reconstruction; EARL2 = EARL2-compliant reconstruction.



Supplementary Figure 5 Heterogeneous cylindrical phantom mimicking high-uptake lesions for defective detector block analysis. (a) Transaxial image of a ring-based cylindrical phantom (diameter $\varnothing = 40$ cm) acquired for 5 min. The high-uptake ring was located at radial positions $R = 13\text{--}15$ cm and contained an $[^{18}\text{F}]$ activity concentration of 11.6 kBq/mL; the background contained 0.6 kBq/mL. (b) VOI-based relative-difference map comparing the central one-detector-electronics-assembly defect pattern (16 DDBs) with the reference dataset; the yellow star marks the 10-mm VOI in the high-uptake ring with the most severe relative difference (RD = -7.7%). DDB = defective detector block; VOI = volume of interest [96].

Declaration of Contribution

The work presented in this thesis was conducted at the Department of Nuclear Medicine and Clinical Molecular Imaging under the supervision of Prof. Dr. Christian la Fougère and Dr. Fabian Schmidt. My individual scientific contributions to each study are summarized below.

Development of an abbreviated dynamic protocol for [^{18}F]FDG parametric imaging

I performed the image reconstruction, post-processing, quantitative and statistical analyses, interpreted the results, and prepared the manuscript [59]. Hasan Sari was responsible for patient recruitment, PET acquisitions, and lesion delineation.

Tumour subtype characterisation using an abbreviated dynamic protocol

I performed the image reconstruction, post-processing, and quantitative data analysis and contributed to the interpretation of the results and manuscript preparation (currently under review). Eduardo Calderón was responsible for patient recruitment, lesion delineation, tumour subtype classification, and assessment of PD-L1 status.

Assessment of respiratory motion artefacts and their correction

I developed the methodological framework, designed and performed the simulations, reconstructed the patient and phantom data, implemented the motion-correction strategies, and conducted the post-processing and quantitative analyses. Patient selection and lesion delineation were performed by Stefan Weigel; the representative lesion model was defined together with Fabian Schmidt. A manuscript was prepared based on the joint work of Stefan Weigel and me and is currently under review.

Robustness of LAFOV PET to defective detector blocks

I designed and performed the simulations and conducted the image reconstruction, post-processing, quantitative evaluation, and statistical analysis. Lesion delineation was performed by Eduardo Calderón. I contributed to the interpretation of the results and preparation of a manuscript (currently under review) in collaboration with Konstantinos Vrakidis.

The contributions of all co-authors are acknowledged both above and in the respective manuscripts.

I hereby declare that I prepared this thesis independently and used no sources or aids other than those explicitly indicated. All contributions from other researchers have been appropriately identified.

Tübingen, 18 June 2026

Wenhong Lan

List of Publications

Research articles

Lan, W., Sari, H., Rominger, A. et al. Optimization and impact of sensitivity mode on abbreviated scan protocols with population-based input function for parametric imaging of [18F]-FDG for a long axial FOV PET scanner. *Eur J Nucl Med Mol Imaging* 51, 3346–3359 (2024). <https://doi.org/10.1007/s00259-024-06745-3>

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Linder, P.M., **Lan, W.**, Calderón, E. et al. Continuous bed motion versus step-and-shoot acquisition in LAFOV PET/CT: insights from multi-phantom and patient studies. *EJNMMI Phys* 13, 33 (2026). <https://doi.org/10.1186/s40658-026-00867-3>

Mannheim, J.G., **Lan, W.**, Conti, M. et al. Feasibility of in vivo small animal imaging using a clinical total-body PET/CT system. *EJNMMI Phys* 12, 71 (2025). <https://doi.org/10.1186/s40658-025-00782-z>

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Pommranz, C.M., Elmoujarkach, E.A., **Lan, W.** et al. A digital twin of the Biograph Vision Quadra long axial field of view PET/CT: Monte Carlo simulation and image reconstruction framework. *EJNMMI Phys* 12, 31 (2025). <https://doi.org/10.1186/s40658-025-00738-3>

Calderón E, Schmidt FP, **Lan W.**, et al., Image Quality and Quantitative PET Parameters of Low-Dose [18F]FDG PET in a Long Axial Field-of-View PET/CT Scanner. *Diagnostics*. 2023; 13(20):3240. <https://doi.org/10.3390/diagnostics13203240>

E. Elmoujarkach, F. P. Schmidt, E. Calderón, **W. Lan.** et al., "PETAL-3D: Progressive Elimination of Noise Toward Accurate Ultra Low-Count PET Images Using 3-D U-Nets," in *IEEE Transactions on Radiation and Plasma Medical Sciences*, vol. 10, no. 6, pp. 837-848, July 2026, doi: 10.1109/TRPMS.2025.3638644.

Trautwein, N.F., Calderón, E., Linder, P.M., Reischl G., Driessen P., **Lan W.**, et al. Low-activity [18F]-somatostatin receptor (SSTR) imaging using [18F]SiTATE on a long axial field-of-view PET/CT scanner. *EJNMMI Phys* 12, 13 (2025). <https://doi.org/10.1186/s40658-025-00720-z>

Conference contributions

W. Lan, S. Weigel, N. Birge, P. Schleyer, C. I. Fougère and F. P. Schmidt, "Precise Tumor and Respiratory Motion Modeling with a Long Axial Field of View PET Simulation Framework: Impact of Voxelization on Lesion Fidelity," 2025 IEEE Nuclear Science Symposium (NSS), Medical Imaging Conference (MIC) and Room Temperature Semiconductor Detector Conference (RTSD), Yokohama, Japan, 2025, pp. 1-2, doi: 10.1109/NSS/MIC/RTSD57106.2025.11286969

W. Lan et al., "Robustness Assessment of Long Axial Field of View PET Performance for Simulated Detector Failures: Insights from a Multiphantom Evaluation," 2025 IEEE Nuclear Science Symposium (NSS), Medical Imaging Conference (MIC) and Room Temperature Semiconductor Detector Conference (RTSD), Yokohama, Japan, 2025, pp. 1-1, doi: 10.1109/NSS/MIC/RTSD57106.2025.11287722

W. Lan et al., "Accelerated Monte Carlo Simulation Framework for Patient Motion Correction with a Long Axial field of view Positron Emission Tomography scanner" 2025 Proceedings of the 11th bwHPC Symposium, Tübingen, Germany, 2025, pp.37-42

W. Lan et al., "A Simulation Framework to Establish Ground Truth for Motion Correction in Total-Body PET: Initial Evaluation for Complex Respiratory Motion," 2024 IEEE Nuclear Science Symposium (NSS), Medical Imaging Conference (MIC) and Room Temperature Semiconductor Detector Conference (RTSD), Tampa, FL, USA, 2024, pp. 1-2, doi: 10.1109/NSS/MIC/RTSD57108.2024.10656116

W. Lan et al., "Impact of the Sensitivity Mode on [18F]-FDG Parametric Imaging for 65-min and 20-min abbreviated Scans with PBIF at the Biograph Vision Quadra PET/CT Scanner" 2024 Total-Body PET conference, Groningen, Netherlands, 2024.

W. Lan et al., " Implementation and Optimization of Short Dynamic Imaging Protocols for Parametric Imaging with a Population Based Input Function for Total-Body PET", 6th GyMIC Molecular Imaging Symposium, Tübingen, Germany, 2023.

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