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Total Body PET/CT: Clinical Value and Future Aspects of Quantification in Static and Dynamic Imaging

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Total body (TB) Positron Emission Tomography (PET) / Computed Tomography (CT) scanners have revolutionized nuclear medicine by enabling whole-body imaging in a single bed position.[1] This review assesses the physical and clinical value of TB-PET/CT, with a focus on the advancements in both static and dynamic imaging, as well as the evolving quantification techniques. The significantly enhanced sensitivity of TB scanners can reduce radiation exposure and scan time, offering improved patient comfort and making it particularly useful for pediatric imaging and various other scenarios. Shorter scan times also decrease motion artifacts, leading to higher-quality images and better diagnostic accuracy. Dynamic PET imaging with TB scanners extends these advantages by capturing temporal changes in tracer uptake over time, providing real-time insights into both structural and functional assessment, and promoting the ability to monitor disease progression and treatment response. We also present CT-free attenuation correction methods that utilize the increased sensitivity of TB-PET as a potential improvement for dynamic TB-PET protocols. In static imaging, emerging quantification techniques such as dual-tracer PET using TB scanners allow imaging of two biological pathways, simultaneously, for a more comprehensive assessment of disease. In addition, positronium imaging, a novel technique utilizing positronium lifetime measurements, is introduced as a promising aspect for providing structural information alongside functional quantification. Finally, the potential of expanding clinical applications with the increased sensitivity of TB-PET/CT scanners is discussed.
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Introduction

Total Body Positron Emission Tomography (TB-PET/CT) is an advanced imaging technique designed to capture high-resolution, comprehensive images of the entire body. While conventional PET scans have taken a significant role in diagnosing and monitoring diseases, they face limitations such as detecting only about 1% of emitted radiation, leading to reduced image quality and lower signal-to-noise ratios. Additionally, their short axial field-of-view (SAFOV-PET) often requires multiple scans to assess widespread disease, increasing scan times and ultimately radiation exposure from the CT.

TB-PET/CT overcomes these limitations by offering simultaneous whole-body imaging without the need for bed translation

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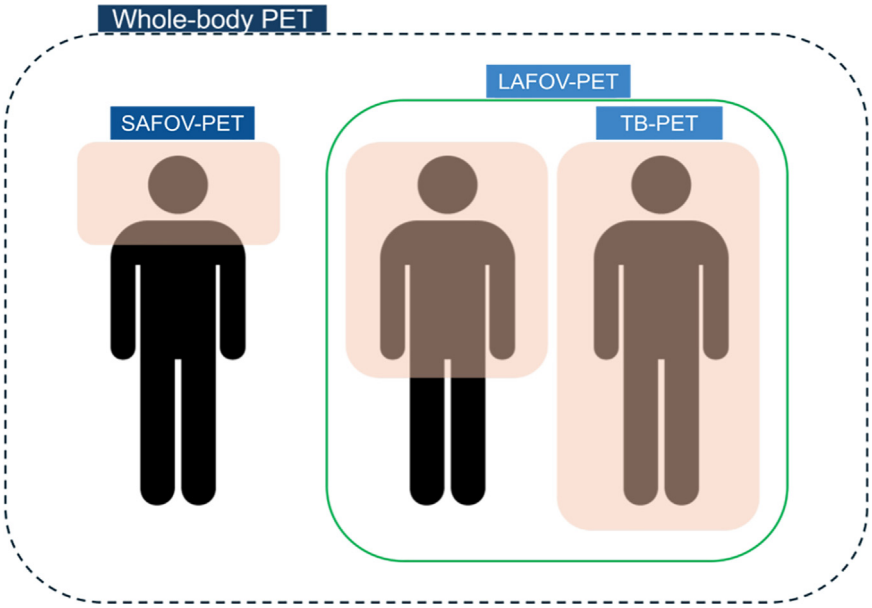

Figure 1 PET/CT scanners can be categorized based on their axial field-of-view (FOV) capabilities, which directly impact their clinical applications. These categories include short-axial field-of-view (SAFOV), long-axial field-of-view (LAFOV), and total-body (TB) imaging systems.[5]

(Fig. 1). This is achieved through a long axial field-of-view (LAFOV-PET), significantly enhancing system sensitivity and enabling dynamic imaging across multiple organs.[2-4] The introduction of multiring systems and improved scintillator materials, such as bismuth germanate (BGO) and later lutetium-based scintillators (LSO and LYSO), together with transition to fully-3D PET systems in the 1990s and the integration of time-of-flight (TOF) technology in the 2000′s marked substantial improvements in sensitivity and spatial resolution of PET scanners.

With axial lengths up to 194 cm, the development of systems like the Biograph Vision Quadra, uEXPLORER and PennPET EXPLORER allows for comprehensive, high-sensitivity imaging in a single scan, improving both clinical efficiency and patient throughput. This advancement represents a paradigm shift in PET imaging, addressing the constraints of conventional PET scanners (Figure 1) and opening new opportunities for clinical and research applications.[6,7] For instance, TB-PET/CT facilitates the use of long half-life tracers, such as Zr in immuno-PET, to track the biodistribution of radiolabeled monoclonal antibodies over several weeks post-administration.[8] This capability allows for insights into kinetics and therapeutic efficacy, positioning TB-PET/CT as a game-changer in early disease detection, characterization, and treatment response monitoring.

The motivation for developing TB-PET/CT systems stems from the need to enhance clinical diagnostics and research capabilities, precisely.[9,10] TB-PET/CT offers several compelling benefits:

(1) **Increased Sensitivity and Image Quality**: The extended axial field of view (FOV) significantly improves system sensitivity, allowing for better image quality even with reduced radiotracer doses. This is particularly beneficial for pediatric imaging and situations where tracer availability is limited.
(2) **Dynamic and Kinetic Studies**: The ability to capture dynamic processes across the entire body enables more accurate studies of tracer kinetics, improving our understanding of disease mechanisms and treatment responses.
(3) **Clinical Efficiency and Patient Throughput**: TB-PET/CT can reduce scan times and increase patient throughput, making it a valuable tool in busy clinical settings. Faster scans also reduce the need for patient sedation, particularly in pediatric cases.

Furthermore, recent quantification techniques, such as dual-tracer imaging, enable simultaneous visualization of different biological processes which remains a challenge with conventional PET. The enhanced temporal resolution of TB-PET/CT also facilitates the exploration of positronium lifetime spectra, potentially yielding more comprehensive information about tissue microstructure and biochemical properties. This review focuses on the significant advancements in quantification techniques, processing algorithms, and integration of artificial intelligence in TB-PET/CT with its transformative potential in molecular imaging in clinical practice.

Dynamic PET Imaging With TB-PET/CT

Dynamic PET imaging enables the acquisition of tracking tracer kinetics in real-time across multiple organs, offering a

more detailed and comprehensive view of physiological processes compared to static PET imaging.[11] The introduction of TB-PET/CT scanners has further expanded the potential of dynamic imaging, offering a wider axial FOV and increased sensitivity, enabling whole-body dynamic studies with improved spatial and temporal resolution. This technology facilitates the assessment of multiorgan interactions and pharmacokinetics, which are relevant in diseases such as cancer and cardiovascular conditions.[12-17]

The analysis of dynamic PET imaging primarily involves the generation of time-activity curves (TACs) and the application of kinetic modeling techniques to interpret these curves. Non-compartmental modeling offers an alternative approach that does not rely on predefined compartments. Spectral analysis, for example, decomposes the TACs into a series of exponential functions and is increasingly used in oncology for managing metastatic cancers. [18,19] The Patlak plot.,[20] another non-compartmental method, has been clinically applied in the evaluation of cardiac sarcoidosis using dynamic PET/CT with ^{18}F-FDG.[21] Together with the unique property of TB-PET/CT, these methods could provide valuable insights into various physiological processes and disease states, enabling more precise diagnosis and treatment planning in clinical settings.[22]

Clinical Applications and Outcomes of Dynamic PET Imaging

In recent years, dynamic PET imaging has demonstrated potential in enhancing disease staging and monitoring, particularly in oncology. For example, a study on prostate-specific membrane antigen (PSMA) imaging in prostate cancer patients utilized SAFOV-PET cameras to capture dynamic sequences.[23] The study demonstrated that dynamic whole-body PET imaging provided improved target-to-background ratios (TBR) in lesion detection, offering promising advancements in cancer diagnostics, treatment planning, and monitoring.[23] Also, there are reports that late imaging of PSMA-ligands might enhance the diagnostic accuracy, which is due to the limits of SAFOV-PET often limited to the pelvic area.[24] If such dynamic imaging helps in the reduction of nonspecific bone uptake as seen in some PSMA tracers remains to be seen.[25] Another study that limited the FOV to the pelvic area investigated the role of kinetic parameters and fractional dimension.[25] While not enabling a higher detection sensitivity, TB-PET/CT could enable the extraction of these parameters throughout the entire body, which could be useful to improve the selection of patients who are referred to radioligand therapy.[26] Dynamic PET imaging has also been helpful in assessing tumor metabolism and therapy response, particularly with[18] F-FDG in oncology. For LAFOV-PET, it was shown that the lesion contrast of Patlak-processed FDG images was improved, while the lesion detectability was not enhanced.[27] Also, the high temporal resolution of LAFOV-PET facilitates Tikhonov deconvolution and can thereby provide a good estimate of the perfusion.[28] In addition, the scan protocols can be shortened to approximately 20 minutes when using the Patlak method and a LAFOV-PET scanner together with a population based input function.[29]

Another significant clinical application of LAFOV-PET is dynamic whole-body imaging with short half-life isotopes like Rb (Fig. 2). For example, such a LAFOV-PET system could be used to perform whole-body dosimetry studies in Rb,[30] which identified the total effective dose to be in the range of 0.50 and 0.76 μSv/MBq.

CT-Free Attenuation Correction in TB-PET for Dynamic Imaging

CT-free attenuation correction represents a significant advancement in dynamic PET imaging by eliminating the need for repeated CT scans and misregistration with CT

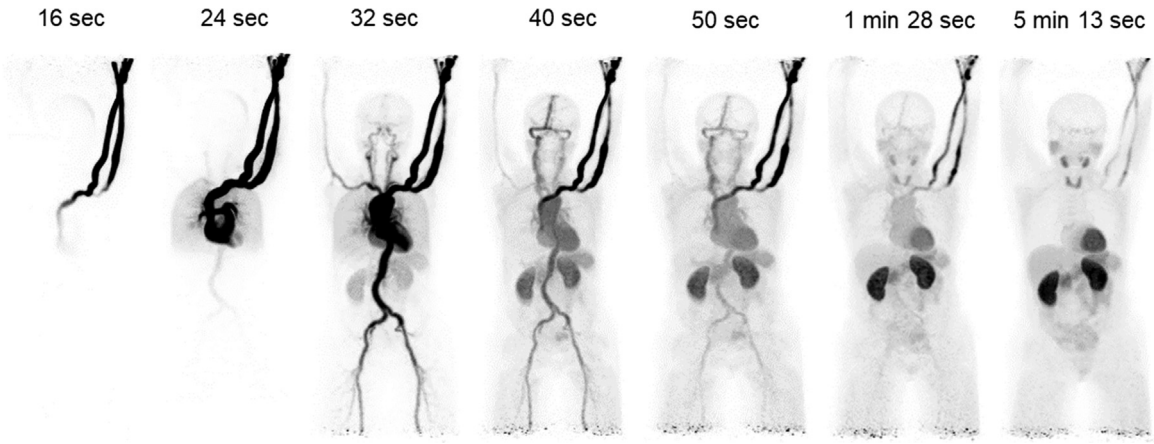

Figure 2 Coronal Maximum Intensity Projection (MIP) images of a. Rb cardiac-perfusion whole-body PET dynamic imaging study. The inflow of the tracer via the left brachial veins is shown in the first image, which is followed by the cardiac passage and systemic distribution. LAFOV-PET enables the visualization of the tracer distribution in one bed position, which facilitates a dosimetric analysis.

images from motion artifacts, which inevitably increase patient radiation exposure. While solely AI-based methods often derive attenuation information directly from PET emission data, providing temporal consistency throughout the acquisition, which is crucial for accurate quantification of tracer kinetics, they ensure that changes in the PET signal are due to actual tracer dynamics rather than artifacts caused by mismatched attenuation correction.[31-33] By inherently accounting for patient motion between and during timeframes, CT-free methods significantly reduce motion artifacts, which is particularly beneficial in long dynamic acquisitions where patient movement is unavoidable.[34] However, purely data-driven approaches might additionally introduce artifacts, since no real transmission scan is acquired.

To overcome these problems, various solutions to CT free PET-attenuation correction have been proposed. Notably, LSO-Tx, a method using background radiation from ^{176}Lu crystals in PET scintillators, coupled with deep learning-based AI, has shown a promising result.[33] The CT-free attenuation correction method using the LSO-Tx scan employs the intrinsic background radiation of the PET detector crystals. [34] Using an open energy window, LAFOV-PET systems can detect these background radiation events, enabling the acquisition of actual transmission scans without the need for additional radiation. While further refinement is needed, particularly through AI, the key advantage of LSO-Tx is the use of real transmission data.

This innovative approach offers a middle ground between fully data-driven corrections and traditional CT-based methods, eliminating the need for additional CT examinations (Fig. 3). The technique is particularly advantageous in scenarios requiring minimize radiation exposure, such as repeated dynamic PET scans or in screening applications where dose reduction is critical. By providing reliable attenuation correction without the added dose burden of CT, this method holds promise for enhancing PET imaging protocols in radiation-sensitive populations.

Benefits of this method include the fact that it is functioning without additional radiation and that the lung geometry better correlates with the PET acquisition, because both have been acquired in a similar mid-respiratory state. In addition, this LSO-Tx-based method allows for ultra-low dose PET exams, reducing the effective dose to approximately 0.15 mSv while maintaining acceptable quantitative accuracy.[33] When paired with LAFOV-PET scanners, this technique achieves a radiopharmaceutical dose more than 50 times lower than the standard effective dose.,[33] which provides a promising potential for screening purposes.

Advanced Static Imaging with TB-PET/CT

In addition to the above discussed benefits of TB-PET/CT for dynamic imaging and its related aspects, in the following we discuss potential benefits in quantification of nondynamic images.

Synergy of Dual-Tracer Imaging and Total Body PET

The extended axial coverage of TB-PET/CT systems permits simultaneous whole-body imaging of both tracers, theoretically capturing their biodistribution and kinetics across multiple organs in a single acquisition.[35,36] Clinically, dual tracer imaging is relevant in various indications. For example, in PSMA-targeted therapy with. Lu (LuPSMA), patients need to be carefully selected to respond to therapy.[33] This is usually done by assessing the PSMA-uptake on PET imaging. In addition, other factors like the degree of bone involvement or tumor volume play a role in outcome prognostication, the latter also in patients not treated with PSMA therapy.[37–40] Changes in PSMA tumor volume in response to therapy are also prognostic.[38,41] It was shown that low PSMA-expression is a negative prognosticator or outcome in patients who receive LuPSMA therapy.[42] However, some groups have

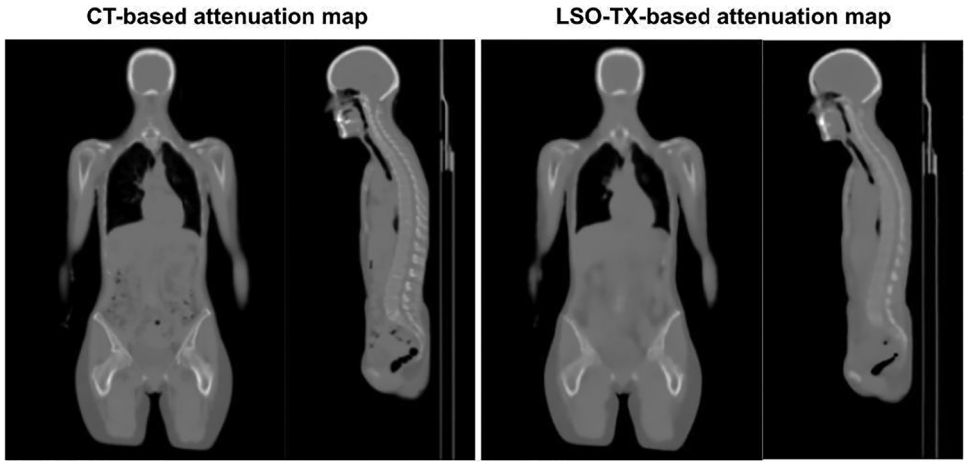

Figure 3 Comparison of attenuation maps using different methods: (Left) Standard attenuation image created by CT-based attenuation. (Right) attenuation image created using an LSO-Tx scan without CT, showcasing CT-free attenuation correction.

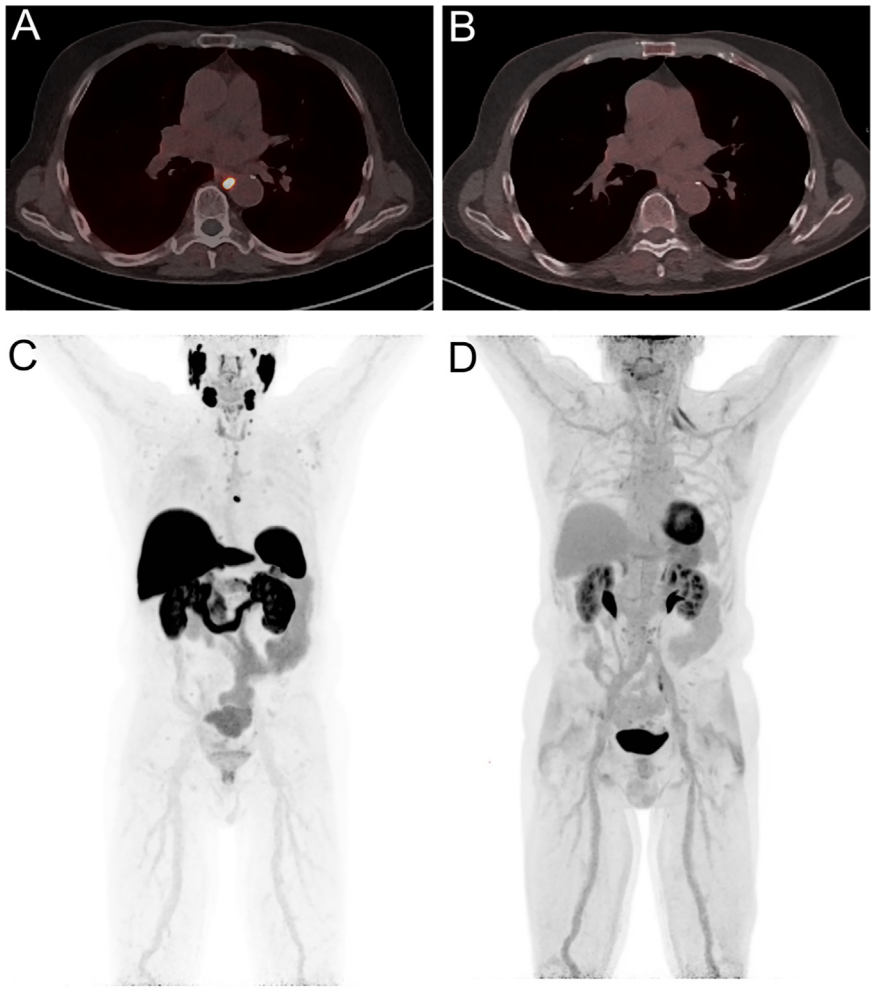

Figure 4 A case study demonstrates the importance of dual-tracer imaging in evaluating eligibility for ^{177}Lu-PSMA therapy. The patients underwent both examinations with an interval of 3 days. The top row shows a lymph node metastasis with strong PSMA-accumulation (A), which had no relevant FDG-accumulation (B). Panel (C and D) depict the representative MIPs of the two PET examinations. No FDG-PSMA mismatch was observed and the patient was referred to LuPSMA therapy. LAFOV-PET could facilitate the acquisition of both examinations by either doing them with no gap between or even simultaneously.

proposed the application of FDG and PSMA imaging to detect also de-differentiated metastases, which have lost the ability to express PSMA.[43,44] These FDG positive, PSMA negative lesions are a negative prognosticator of outcome and a reason to exclude the patient from PSMA therapy. However, in routine clinical practice, the management of patients to acquire two PET scans is difficult (Figure 4). Therefore, a one-day acquisition protocol has been introduced on a LAFOV-PET system.[45] First, the patients underwent regular ^{68}Ga-PSMA-11 PET, followed by a low dose FDG-PET.[45] The FDG-PET shows the PSMA-PET in shine through artifacts, but still this procedure led to the identification of a FDG-positive, PSMA-negative metastasis.[45] This is greatly facilitated by the high sensitivity of LAFOV-PET systems. Another step towards dual tracer imaging is the simultaneous administration of two ligands with distinct radioisotopes and differentiate them by the prompt gamma emission.[46,47] However, the clinical validation of such approaches is still pending.

Positronium Imaging

Positronium imaging represents an innovative frontier in medical imaging, particularly when combined with TB-PET/CT systems (Fig. 5).[48] The extended axial FOV and increased sensitivity of TB-PET/CT systems make them particularly well-suited for positronium imaging, enabling whole-body assessment of positronium lifetimes with improved temporal resolution. This technique uses the unique properties of positronium, a short-lived bound state formed between a positron and an electron, to provide additional structural information about tissues at the nanoscale level. In a vacuum, positronium has a well-defined lifetime of approximately 125 picoseconds, but this lifetime is shortened when positrons interact with the dense electron cloud within tissues.[49] By measuring the time between positronium formation and annihilation, positronium imaging offers insights into tissue characteristics, such as tissue oxygenation levels, which are crucial for understanding cellular metabolism and disease

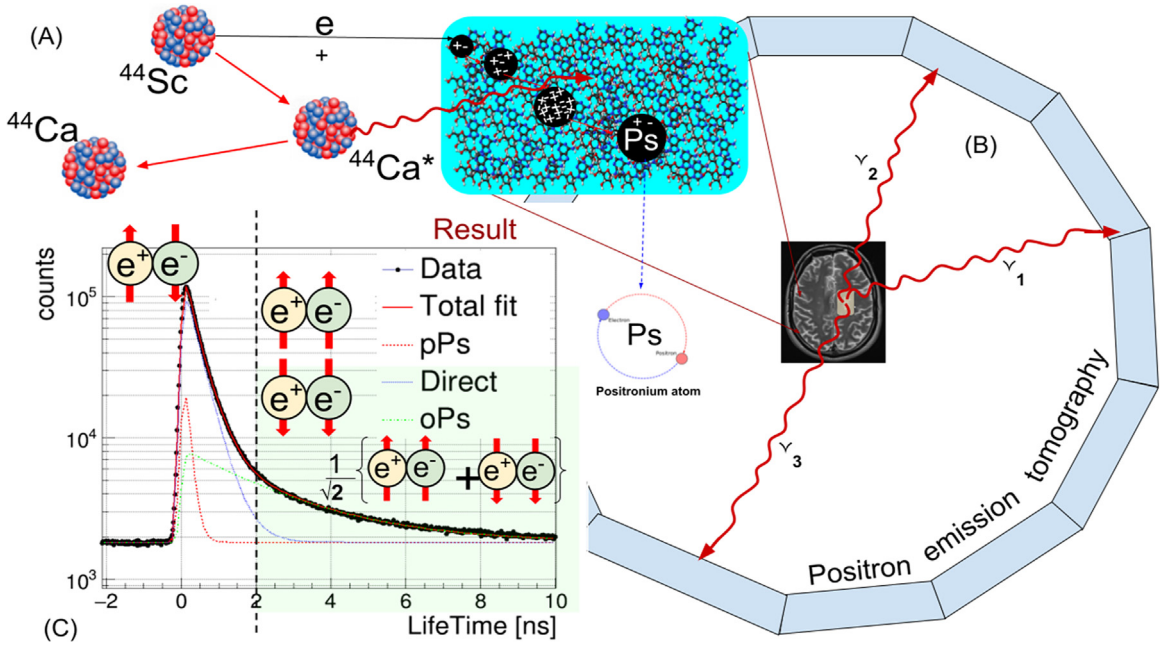

Figure 5 Decay scheme of ^{44}Sc and positronium lifetime imaging in a brain sample (A) The left (top) panel illustrates the decay process of the ^{44}Sc isotope^{44}Sc undergoes beta-plus decay, transforming into an excited state of ^{44}Ca (^{44}Ca*).[50,51,56] This excited nucleus promptly de-excites to its ground state, emitting a characteristic gamma photon (γ), represented by a red arrow. The complete decay can be summarized as: $^{44}\text{Sc} \rightarrow {}^{44}\text{Ca}^* + \text{e+} + \text{v} \rightarrow {}^{44}\text{Ca} + \gamma + \text{e+} + \text{v}$, where e+ is a positron and v is a neutrino. (B) The right panel displays a PET detector with a brain sample, highlighting a colored region representing a tumor or carcinogenic area from which three gamma rays were emitted. γ_1 is de-excited, while γ_2 and γ_3 are annihilation photons. The difference in the average time between γ_2 and γ_3, and γ_1 reveals the positronium lifetime distribution. This innovative imaging technique offers insights into tissue microstructure and potential pathological changes by visualizing positronium dynamics. (C) semi-logarithmic graph depicting the time distribution between the de-excitation photon and annihilation photons from the sample. The plot features a prominent prompt peak, representing para-positronium decay (opposite spin) and direct annihilation events. Beyond 2 ns, the graph illustrates various contributions from the emission site, including ortho-positronium (parallel spin), pick-off annihilation, and self-annihilation processes. This time-resolved spectrum provides valuable insights into positronium formation and decay dynamics within the sample, enabling the differentiation of various annihilation modes and their respective lifetimes.

progression, that may not be visible through standard PET scans.[50,51] The advancements in positronium lifetime image reconstruction for TOF PET elevate the ability to assess hypoxia, which is a significant factor in conditions like tumors, ischemic heart disease, and neurodegenerative disorders.[52-55] The extended axial FOV and increased sensitivity of TB-PET/CT systems make them particularly well-suited for positronium imaging, enabling whole-body assessment of positronium lifetimes with improved temporal resolution.

The potential applications of positronium imaging in oncology are especially promising when implemented on TB-PET/CT platforms. Tumors often exhibit altered tissue density and microenvironment compared to healthy tissues, affecting the lifetime of positronium and potentially allowing for more accurate identification and characterization of malignancies.[57-59] The combination of metabolic information from conventional PET scans with structural insights at the nano-scale level could enable an improved cancer characterization.[59]

To implement positronium lifetime imaging, radiopharmaceuticals that emit an additional photon besides the standard annihilation photons are required, such as ^{44}Sc,^{66}Ga, or ^{94}Tc (for physics experiments) and ^{124}I, ^{68}Ga (clinical purposes).[56] The process involves detecting the initial de-excitation photon from the radioisotope, followed by the detection of the subsequent annihilation photons, and calculating the time difference to estimate positron lifetime.[53] TB-PET/CT systems, with their improved timing resolution and extended coverage, are particularly adept at capturing these complex decay schemes across the whole body. Collected positron lifetime spectra in each voxel of the image can be analyzed to estimate mean positronium lifetime, potentially revealing structural changes in tissues not visible through standard PET imaging alone.[56]

The first in-vivo positronium image of the human brain was recently demonstrated with the multiphoton J-PET scanner.[55] The concept of positronium imaging has shown promising results in phantom studies in a clinically employed LAFOV-PET scanner.[61] In addition, a study by Qi and Huang (2022)[62,63] developed a new reconstruction method for positronium lifetime images, which may enable high-resolution imaging of the tissue microenvironment.[53] Moreover, a study by Takyu et al.[61] highlighted the ability of positronium imaging to distinguish between hypoxic and normoxic tissues based on oxygen levels, which could be relevant in both cancer and cardiovascular disease management.

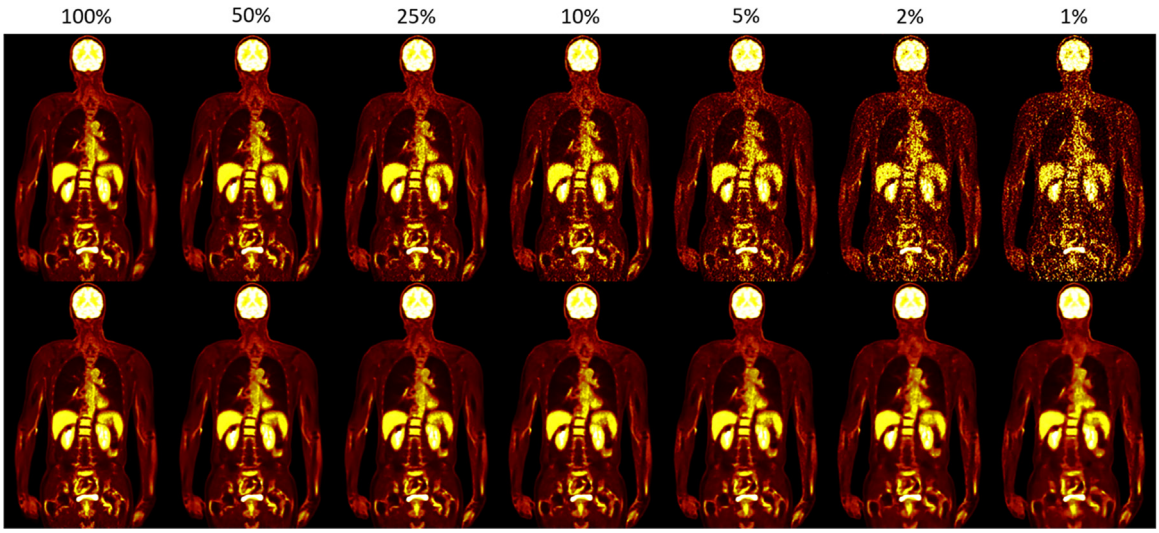

Figure 6 Input images of shorter scan time (the first row) and the predicted full dose (ie denoised) images generated using UNet3D (the second row). Note that all the images were normalized by the total injected activities.

Positronium's sensitivity to hypoxia offers a potential method for detecting and characterizing regions of low oxygenation in tumors or other tissues.[60] However, future trials are mandatory to assess the biological relevance and clinical feasibility of in vivo positronium imaging.

AI's Application in Total Body PET

Artificial intelligence (AI), especially deep learning, has been increasingly applied in TB-PET/CT, to reduce scan time, improve image quality, and enhance diagnostic accuracy.[64] Deep learning models, such as convolutional neural networks and diffusion models, can be used to denoise PET images, thus reconstructing high-quality images from PET scans of lower radiotracer doses or shorter scan times.[64–67] With the high sensitivity of TB-PET/CT, these models can further reduce scan time while maintaining diagnostic quality, with only 10% of the original scan time. Fig. 6 shows some AI-reconstructed images generated from PET scans of different scan time reduction factors ranging from 1% to 50%. As the scan time becomes shorter, the AI-recovered PET images become blurrier, but the images recovered from a reduction factor larger than 10% are visually acceptable for diagnostics. As for image quality improvement, the high-resolution images from TB-PET/CT scanners, such as uEXPLORER, can help optimize the quality of images from short-axis PET scanners through deep learning while controlling costs.[68]

Conclusion and Future Outlook

TB-PET/CT has greatly impacted nuclear medicine by enabling high-resolution, whole-body imaging in a single bed position. This advancement significantly enhances the ability to capture dynamic processes across multiple organs simultaneously, which enables kinetic modeling or model-free approaches to dynamic imaging. The utilization of background radiation that is present in the PET detector crystals can be used to acquire attenuation correction maps, which can be beneficial for repeated scans in dynamic imaging scenarios or for low dose PET examinations. Positronium imaging, when combined with TB-PET/CT, adds another layer of detail by revealing structural information at the nanoscale, which might help to assess the oxygenation level of the tissue.

Looking forward, the synergy between TB-PET/CT and artificial intelligence is expected to further enhance the clinical feasibility of molecular imaging. AI-driven technologies are expected to enhance image quality and reduce scan times, which is particularly applicable to the high sensitivity TB-PET/CT examinations. Multi-tracer imaging in TB-PET/CT systems could enable simultaneous investigation of diverse biological processes, leading to more holistic and personalized diagnostic approaches. In the near future, these developments could establish TB-PET/CT as a reference standard in diagnostic imaging, with capabilities that significantly enhance early detection, treatment planning, and overall patient care compared to conventional PET.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Narendra Rathod reports financial support was provided by University of Bern. Narendra Rathod reports a relationship with University of Bern that includes: employment. I am Narendra Rathod working as a Post-doc in University of Bern is my relation with the University and hence with the funding grants. If there are other authors, they declare that they have no known competing financial interests or personal

relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Narendra Rathod: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Warissara Jutidamrongphan:** Writing – review & editing. **Wolfram Andreas Bosbach:** Writing – review & editing. **Yizhou Chen:** Writing – review & editing, Writing – original draft, Data curation. **Jan Luca Penner:** Writing – review & editing. **Hasan Sari:** Writing – review & editing, Resources. **Konstantinos Zeimpekis:** Writing – review & editing, Validation, Resources, Conceptualization. **Alejandro López Montes:** Writing – review & editing. **Pawel Moskal:** Writing – review & editing. **Ewa Stepien:** Writing – review & editing. **Kuangyu Shi:** Writing – review & editing, Resources. **Axel Rominger:** Writing – review & editing. **Robert Seifert:** Writing – review & editing, Supervision, Resources, Conceptualization.

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