Positron Emission Tomography (PET) is a pivotal molecular imaging technique that is essential for the non-invasive evaluation of various diseases in vivo. Within the realm of clinical oncology, PET's utilization is crucial across numerous phases including diagnosis, staging, restaging, assessment of therapeutic response, and in the orchestration of radiation therapy. The imperative for high-quality imaging with minimal artifacts is clear, as these factors are fundamental for both the qualitative interpretation and the quantitative analysis of PET scans.

Artifacts in PET imaging are anomalies in the final images that do not correspond to the true distribution of the radiotracer within the body. These can be caused by a variety of factors, including patient motion, improper scanner calibration, and physiological processes that interfere with signal acquisition. Artifacts can lead to misinterpretations in clinical diagnosis, making it essential to identify and correct them to enhance the accuracy of PET scans.

However, the presence of artifacts in medical imaging still is a recurring challenge that may impair image fidelity and quantitative reliability, potentially leading to erroneous interpretations that could adversely influence clinical decisions.

Scatter correction is a technique used to enhance the quality of PET images by removing scatter radiation that can blur images and obscure details. During a PET scan, photons emitted by the radiotracer can scatter as they collide with other particles before reaching the detectors. This scatter distorts the image by introducing signals from incorrect locations. Scatter correction algorithms estimate the amount of scattered photons and subtract them from the detected signals, thereby improving image clarity and contrast.

Attenuation correction is another critical process in PET imaging, which compensates for the loss of signal intensity due to the absorption of photons within the body. Different tissues absorb photons at varying rates, which can lead to underestimation of tracer concentration in areas like bones or organs with higher density. Attenuation correction uses data from a transmission scan (using either a radioactive source or a CT scan) to accurately map the absorption properties of various tissues and adjust the PET signal accordingly. This correction is crucial for providing quantitatively accurate images that reflect the true distribution of the radiotracer.

Attenuation and scatter correction (ASC) are critical during PET image reconstruction, primarily aimed at enhancing image clarity and accuracy. However, the implementation of these corrections can inadvertently introduce artifacts, especially when dealing with complex scenarios like high radiotracer activity or patient movement.

Common artifacts encountered in PET imaging can be categorized as follows: (i) those associated with the distribution of the tracer, such as halo artifacts; (ii) those that arise from the alignment of PET with CT or MR images, including mismatch, misregistration, or motion artifacts; and (iii) those transmitted from CT or MRI to PET images, such as errors caused by metals, contrast agents, and image truncation.

**Halo artifacts** in PET imaging notably prevalent with gallium-68 (68Ga)-labeled compounds, represent a significant challenge in accurately interpreting high-activity regions adjacent to organs. In fact, these are a Radiopharmaceutical-related artifact category which arise from excessive radiopharmaceutical accumulation and complicate the evaluation of adjacent tissues.

These artifacts are primarily induced by incorrect scatter correction during image reconstruction, where negative values near regions of intense radiopharmaceutical accumulation—such as the bladder or kidneys due to urinary excretion of the tracer—lead to the assignment of zero values to these voxels due to the non-negativity constraint in statistical reconstruction algorithms. This phenomenon results in the formation of a "halo" or photopenic area around these high-activity zones, potentially obscuring faint abnormalities and impacting the diagnosis, staging, and treatment planning for cancer patients. The presence of halo artifacts, particularly near primary tumors or areas prone to local recurrences in pelvic cancers, poses a risk of misdiagnosis by masking or altering the visual and quantitative interpretation of PET images. Efforts to mitigate these artifacts, such as the administration of diuretics, often result in increased patient discomfort and the potential for motion artifacts, further complicating the image quality and interpretability.

Most PET acquisition settings are performed with arms up (to decrease photon scater). But raising the arm is uncomfortable for patients, resulting in arm motion during sequential PET and CT/MRI scans. This is one of the example of mismatch effect.

**Mismatch** artifacts represent a significant challenge in PET imaging, particularly when discrepancies arise between PET and anatomical scans such as CT or MRI. These discrepancies can stem from both voluntary and involuntary movements of organs, potentially leading to the misidentification, mislocalization, and inaccurate quantification of lesions. This issue is critical as it can result in misdiagnoses and, subsequently, inappropriate patient management. Techniques such as deformable image registration have been developed to mitigate these effects, though they cannot always completely eliminate the problem. The occurrence of mismatch artifacts necessitates a nuanced approach to PET imaging, incorporating strategies like different CT acquisition protocols to minimize potential misalignments.

**Truncation artifacts** in PET imaging emerge primarily due to the disparities in the transaxial fields of view (FOVs) between PET and CT/MRI modalities. These artifacts are particularly prevalent in scenarios involving obese patients, or when patients have their arms down during the scanning process, as well as in cases where PET/CT or PET/MR scans are utilized for treatment planning. The essence of truncation artifacts lies in the absence of corresponding parts of the attenuation map for structures that extend beyond the CT/MR images, leading to inaccuracies in standardized uptake value (SUV) estimations—typically, an overestimation at the periphery and an underestimation towards the center of the image. The issue is compounded when anatomical images truncate parts of the patient's body, leading to artifacts and distorted activity quantification in PET images. Optimally positioning the patient in the center of the FOV with arms raised can mitigate such artifacts, yet specific conditions, like scanning for melanoma or head-neck cancer, necessitate arms-down positioning. Various strategies, including extended FOV CT scans, extrapolation of CT projections, specialized MR sequences, and manual or semi-automatic in-painting algorithms, have been explored to address or alleviate truncation artifacts. Despite these efforts, managing truncation artifacts remains a complex challenge, especially in overweight patients where increased photon attenuation and scattering further degrade image quality and quantitative accuracy.

Halo and mismatch artifacts are notably frequent in PET imaging using gallium-68 (68Ga)-labeled radiopharmaceuticals. These artifacts might be overlooked if they are subtle, yet when pronounced, they can significantly degrade the image quality, necessitating additional scans. However, even repeated scanning often fails to correct these artifacts, as they are sometimes inherent and unavoidable in specific situations.

While attenuation and scatter correction techniques are indispensable for producing reconstructed and quantitative PET images, their role in the occurrence of certain artifacts necessitates a nuanced approach to PET imaging. Understanding the limitations and potential pitfalls of these techniques is crucial for radiologists and clinicians in interpreting PET images accurately. Ensuring meticulous calibration, considering patient-specific factors, and using advanced correction algorithms are essential steps in minimizing the impact of these artifacts on clinical outcomes.

The production of quantitatively precise and visually decipherable PET images necessitates the integration of CT or MRI for effective attenuation and scatter correction (ASC). Typically, an unenhanced, low-dose CT scan is conducted alongside PET/CT scans for ASC, and occasionally, a diagnostic CT scan with a contrast agent may serve the same function. Elimination of the CT component could be particularly beneficial for patients requiring repeated PET/CT scans, notably pediatric patients, as even marginal reductions in cumulative radiation exposure are of significance.

In the quest to improve ASC, deep learning (DL) has emerged as a groundbreaking approach, offering innovative strategies to surmount traditional challenges. DL-based methods have been developed for various ASC applications in PET imaging, including the synthesis of pseudo-CT images from MRI or uncorrected PET data, prediction of scatter maps from emission data, and direct generation of ASC PET images from non-ASC-corrected inputs, all demonstrating the vast potential of DL in enhancing the safety and efficacy of PET imaging.

The integration of computed tomography (CT) in PET/CT imaging, while invaluable for attenuation correction (AC) and precise anatomical localization, significantly contributes to the total ionizing radiation dose received by patients. Innovations such as long axial field of view (LAFOV) total-body PET scanners have markedly improved image resolution and quantification while reducing the need for high radiopharmaceutical doses. Nonetheless, the aspiration for entirely CT-free PET imaging methodologies is driven by the imperative to diminish radiation exposure in vulnerable populations and during repeated examinations or longitudinal studies.

Historically, the field has seen progress through magnetic resonance (MR)-based strategies and algorithmic advances such as the maximum likelihood estimation of activity and attenuation (MLAA), further refined with time of flight (TOF) enhancements. Despite these developments, the interplay between activity distribution and attenuation remains a challenging frontier, compounded by scanner-specific noise and resolution discrepancies. In this complex landscape, deep learning (DL) presents a promising paradigm capable of transcending these limitations. However, the success of DL in PET imaging critically hinges on its adaptability to the dynamic nature of PET tracers, particularly Ga-68, and the variability across imaging platforms.

Yet, the quest for CT-free PET imaging avenues, particularly beneficial in pediatric scans, repetitive examinations, and pharmaceutical research, underscores the need for novel correction techniques devoid of additional radiation risks.

The realm of CT-free PET correction has seen advancements through magnetic resonance (MR)-based methodologies and the development of algorithms such as the maximum likelihood estimation of activity and attenuation (MLAA) enhanced by time of flight (TOF) data. Despite these strides, the challenges of activity-attenuation crosstalk and noise persist, propelling the exploration of deep learning (DL) solutions tailored to surmount these hurdles. However, the efficacy of DL approaches in PET imaging faces limitations due to scanner variability, evolving tracers with unique biodistributions, and the heterogeneity inherent in PET imaging domains. This predicament necessitates the development of a deep learning model that transcends center-specific and tracer-specific constraints, offering a universally applicable solution for Ga-68 PET imaging.

The study introduces an innovative approach to deep learning for CT-free PET imaging, effectively integrating domain knowledge to handle the heterogeneity of PET tracers and scanners. By simplifying the complex challenge into domain decomposition, it preserves high-frequency textures while robustly learning low-frequency, anatomy-dependent corrections, demonstrating effectiveness across various tracers and scanners. [oon maghale aslie]

Addressing these complexities, this study introduces a pioneering deep learning methodology that operates independently of imaging centers and the diverse characteristics of Ga-68 radiotracers. Our approach leverages the expansive capabilities of DL to generate attenuation maps or pseudo-CT images directly from non-corrected PET scans, thereby facilitating CT-free PET image correction. By integrating a deep learning framework that is adaptive to various Ga-68 applications and resilient to the idiosyncrasies of different PET scanners, we aim to eliminate the dependence on CT for AC, offering a groundbreaking avenue for radiation-free, accurate PET imaging. This innovation not only promises to enhance the safety and efficacy of PET diagnostics but also paves the way for its broader application in clinical and research settings, particularly where reducing radiation exposure is critical.

This investigation introduces an innovative deep learning framework designed to be agnostic to the specificities of imaging centers and the unique biodistribution profiles of Ga-68 labeled tracers. Our methodology revolutionizes the approach to PET image correction by leveraging deep learning to infer attenuation maps or pseudo-CT images directly from non-corrected PET scans. This strategy enables a robust, CT-free correction process, eliminating the additional radiation burden associated with conventional CT-based AC.

Central to our approach is the development of a DL model that is not only resistant to the challenges posed by scanner diversity and tracer variability but also capable of generalizing across different Ga-68 applications. This model represents a significant leap forward in the field, offering a universally applicable, scalable solution that paves the way for safer, more efficient PET imaging. Through comprehensive training on diverse datasets, this model is fine-tuned to accurately predict and correct PET images, ensuring high fidelity and quantitative accuracy across a broad spectrum of clinical and research scenarios.

In summary, by addressing the pivotal challenges of radiation exposure, tracer variability, and scanner heterogeneity, our study sets a new benchmark for PET imaging. It not only enhances the practical utility and safety of Ga-68 PET diagnostics but also significantly broadens its applicability in precision medicine and pharmaceutical development, heralding a new era of radiation-free, highly accurate molecular imaging.