

Supplementary Materials

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Supplementary Methods

Preparation of CT-free PET frameworks

As a common starting point for all frameworks, PET list-mode data were binned into three-dimensional sinograms. For patient scans acquired with protocols A and B, coincidence events of the full 8-minute acquisitions were used. For the dynamic PET protocol C, we only selected coincidence events recorded within the time window of 57 to 65 minutes post injection. In addition, for the construction of CT-based μ -maps (μ_{CT}), LD-CT data was firstly used to reconstruct CT-images with the maximum-likelihood transmission reconstruction (MLTR) algorithm (1) and then subsequently converted into μ -values for 511 keV photons. Both algorithms were implemented in e7-tools (Siemens Healthineers, Knoxville, TN).

LSO-Tx based framework

Lutetium-176, an electron-emitting radioisotope with a half-life of 3.7×10^{10} years, is naturally contained in LSO crystals. The emitted electron locally deposits a maximum of 597 keV within each LSO crystal, while the daughter nucleus is de-excited by emitting a cascade of gammas. Following the methodology described by Teimoorisichani et al. (2), captured events due to the decay of Lu-176 were initially histogrammed in non-TOF sinograms, which were then used to generate μ_{LSO-Tx} using the MLTR algorithm (1). The blank LSO-Tx data required by the methodology were acquired from a 6-hour LSO-Tx acquisition prior to any patient data collection.

Data pre-processing for CNN training

Paired non-attenuation-corrected PET images (NAC-PET) and μ_{CT} from the 114 patients that underwent the clinical protocol A were used for the development of CNN-based framework. These were separated into training and validation sets of 100 and 14, respectively.

NAC-PET images were reconstructed using a three-dimensional TOF ordinary Poisson ordered subsets expectation-maximization (OP-OSEM) algorithm (3) implemented in e7-tools with point-spread-function modeling, 4 iterations, 5 subsets, maximum ring difference of 85, with a 4 mm isotropic Gaussian filtering, along with corrections for random coincidences, crystal efficiency, detector dead time, decay and frame-length. The resulted NAC-PET images and μ_{CT} , with dimensions $440 \times 440 \times 645$ voxels of size $1.65 \times 1.65 \times 1.64$ mm³, were zero-padded and down-sampled to $224 \times 224 \times 336$ voxels by doubling the voxel size.

With NAC-PET images having units proportional to the number of acquired coincident events (prop. cps), large intra- and inter- patient variability in voxel intensities and image contrasts were observed. These are possibly attributed to differences in tracer uptake, injected activities, time elapsed between the injection and the scan, and different magnitudes of attenuation for each patient, most of which NAC-PET images don't account for. To mitigate these variabilities and enhance image contrast, we performed a series of processing steps:

First, NAC-PET images were converted to units proportional to activity concentration, cps/ml, by dividing them by the voxel volume V , followed by a normalization step using the following equation:

$$NAC-PET' = \frac{NAC-PET}{V} \cdot \frac{W}{C}$$

where C is the injected activity in becquerels and W the weight in kg. Hyperbolic tangent functions were used as following:

$$\text{NAC-PET}'' = \tanh\left(\frac{\text{NAC-PET}'}{\tanh(\text{NAC-PET}') + a}\right)$$

With parameter a being empirically set to 0.5. Subsequently, to enhance soft-tissue contrast, multidimensional contrast limited adaptive histogram equalization (MCLAHE) method (4) was used with a $96 \times 96 \times 96$ voxel kernel and a clip limit of 10^{-3} . An unsharped masking technique was applied for further edge enhancement, by subtracting from the starting image the blurred version obtained by a Gaussian filtering of 6 standard deviations multiplied by a factor of 0.4. Lastly, another run of MCLAHE was executed with $96 \times 96 \times 96$ voxel kernel and a clip limit of 10^{-2} . μ_{CT} were normalized by the μ -value of 0.15 cm^{-1} , which corresponds to the typical linear attenuation coefficient of skull bone for 511 keV photons.

CNN training

The chosen CNN architecture was a three-dimensional (3D) attention-gated U-Net (5) as implemented in MONAI (version 1.3.0) (6), which is an open-source library based on PyTorch (7). The network comprised five levels with 16, 32, 64, 128, and 256 channels. Feature extraction used $3 \times 3 \times 3$ convolution kernels, with stride-2 convolutions for down sampling and $3 \times 3 \times 3$ stride-2 transposed convolutions for upsampling. The training took place using 3D patches of $128 \times 128 \times 128$ voxels, without data augmentation, with a batch size of 8, Adam with decoupled weight decay (8) as the optimizer and with L1 as the loss function. Training over all data was repeated for 4000 epochs, with an initial learning rate was set at 10^{-4} , and a learning scheduler reducing that rate by half when the validation loss did not decrease for 100 epochs. By the end of the training, the scheduler was triggered 13 times, with the final learning rate being 1.2×10^{-8} .

Evaluation of CNN-based Framework

Performance assessment of the trained CNN was based on data obtained from the 12 patient scans that underwent whole-body ^{18}F -FDG PET/CT imaging protocols B and C, which were not used for the CNN training. For that purpose, NAC-PET images and μ_{CT} were generated and processed following the same steps described for the training data. Eventually, the original grid size of $440 \times 440 \times 645$ voxels was restored by cropping and interpolating the inferred μ_{CNN} by using 3rd degree polynomial interpolation.

Joint-reconstruction algorithms

The implementations of TOF-enabled MLAA and MLACF algorithms that were used are described in detail at the work of Teimoorisichani et al. (2). Fixed parameters across all patients and mu-maps priors were used for their execution. MLAA reconstruction used 20 global iterations, during each the activity was updated with one iteration and two subsets, and the attenuation image was updated with three iterations and two subsets. For MLACF, 30 global iterations were used, each with activity updates of one iteration, two subsets, and attenuation-factor coefficient (ACF) updates of three iterations. To obtain μ -values in image space, the final ACFs were reconstructed using eight iterations and five subsets. The regularization parameter that modulates the influence of the prior was set to 0.1 for both MLAA and MLACF. The scatter estimations that were based on the μ_{LSO-Tx} or μ_{CNN} and used in MLAA and MLACF, were calculated based on the 3D TOF single scatter simulation (SSS) algorithm (9) implemented in e7-tools with relative scaling. An isotropic Gaussian filter of 4 mm was applied on all output μ -maps. The activity images estimated by MLAA and MLACF were not used because their intensity scales differed from those of the CT-based AC-PET images (2).

PET reconstructions

An additional processing step was executed for all μ -maps obtained with CT-free frameworks prior to the final PET reconstructions. Voxels in μ -maps containing components of the generated patient bed were overwritten with μ -values of a template patient bed, after matching their coordinates with template matching. Activity images with applied attenuation and scatter corrections (AC-PET) based on emission data and the produced μ -maps were reconstructed using e7-tools for further investigations. These reconstructions were performed using a 3D TOF-OP-OSEM algorithm (3), with point-spread-function modeling, using 4 iterations and 5 subsets and maximum ring difference of 85. The scatter component was calculated based on each μ -map by using 3D TOF-SSS algorithm (9) with relative scaling. Additional corrections for random coincidences, crystal normalization, detector dead time and decay and frame-length were applied.

The impact of low-attenuating objects

Low-attenuating objects (μ -values $< 0.015 \text{ cm}^{-1}$), such as head or leg stabilization equipment, patient hair, clothing, and patient bed are not reliably generated in μ -maps of the investigated CT-free frameworks. Meanwhile, these objects contribute to the attenuation and scatter of the emission data, eventually influencing the final quantification. To investigate the impact of these objects on PET quantification, an additional analysis was performed over all patients of the test dataset.

First, we isolated all low-attenuating objects in μ_{CT} by setting to zero all voxels that belong to two body masks, an AC-PET-based one ($SUV > 0.01$) and a μ_{CT} -based one (μ -values > 0.05 , and binary hole-filling), in order to handle potential PET-CT misalignments. Then, for all μ -maps generated from the CT-free frameworks, we replaced the original voxel values with the ones of these low-attenuating objects. This process was also performed on the μ_{LSO-Tx} and μ_{CNN} before being used as priors in MLAA or MLACF, subsequently affecting the final μ -maps also within the body contours due to differences in convergence. Eventually, these modified μ -maps were used for attenuation & scatter corrections during the PET reconstructions, and were compared to the corresponding CT-free ones. By essentially inserting patient scan-specific CT-based information to the μ -maps, this analysis no-longer represents CT-free PET imaging frameworks.

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Supplementary Tables

Supplementary Table 1
Patient groups used in the study

Purpose	Cohort size	Time-interval between PET and CT	Protocol	Sex (M/F)	Age (years)	Weight (kg)	BMI	Injected Activity (MBq/kg)	Dice Score of PET-CT Body Contours	<i>P</i> -value of Mann-Whit. U Test from Protocol A
CNN Training	100	Short	A	52/48	64±13	74.3±13.4	24.6±3.9	3.2±0.7	0.978±0.006	N.A.
CNN Validation	14	Short	A	6/8	60±14	77±15.7	25.1±4.1	3.1±0.8	0.978±0.005	N.A.
Overall	114			58/56	63.4±12.9	74.7±13.8	24.7±3.9	3.1±0.7	0.978±0.006	N.A.
LSO-Tx, Analysis	5	Short	B	0/5	53.8±8.3	63.4±7.8	23.6±2.9	3.2±0.4	0.978±0.008	0.266
	7	Long	C	4/3	62.4±10.9	79.2±20.6	26.1±4.3	3.1±0.1	0.956±0.015	<0.001
Overall	12			4/8	58.8±10.8	72.3±18.3	25±4	3.1±0.3	0.966±0.016	<0.001

Supplementary Table 2
Information of lesion VOIs used in the quantitative analysis

Patient	Protocol	Disease	Lesion VOIs			
			No.	Location	Volume (ml)	Voxels*
1	C	T-cell lymphoma	1	Axillary lymph node	2.3	506
			2	Axillary lymph node	0.3	66
			3	Thyroid	0.5	101
2	C	Multiple myeloma	1	Sternum bone	1.7	375
			2	Axillary lymph node	0.04	9
			3	Sternum bone	0.7	153
3	B	Breast cancer	1	Liver	0.7	148
			2	Ilium bone	0.3	71
			3	Abdominal lymph node	0.1	14
4	B	Breast cancer	1	Left salivary gland	0.4	88
			2	Lumbar vertebra	0.4	82
			-	-	-	-
5	B	Breast cancer	-	-	-	-
			-	-	-	-
			-	-	-	-
6	C	Breast cancer (metastized)	1	Lumbar vertebra	0.7	160
			2	Heart	2.0	437
			-	-	-	-
7	C	Multiple myeloma	1	Rib bone	3.0	677
			2	Femur bone	3.0	671
			3	Rib bone	1.2	260
8	B	Breast Cancer	1	Skin shoulder	0.5	107
			-	-	-	-
			-	-	-	-
9	C	Mutiple myeloma	1	Rib bone	1.9	413
			2	Thoracic vertebra	0.6	133
			3	Cervical vertebra	4.4	992
10	C	Melanoma	1	Armpit	2.9	637
			2	Lymph node neck	0.8	177
			-	-	-	-
11	C	Langerhands cell histiocytosis	1	Skull bone	0.1	20
			2	Ischium bone	1.0	233
			3	Hip bone	0.8	178
12	B	Breast cancer (metastized)	1	Liver	10.0	2223
			2	Cervical vertebra	0.8	171
			-	-	-	-
Mean (SD)				1.5 (2.0)	337 (442)	

*Voxel size: 1.65 mm x 1.65 mm x 1.65 mm

Supplementary Table 3
Results of the blinded qualitative evaluation

Trained Reader's Responses

Patient	Sample A: $AC\text{-}PET_{CT}$			Sample B: $AC\text{-}PET_{CNN}$			Sample C: $AC\text{-}PET_{CNN}^{MLACF}$		
	Assigned	Reader	Classification	Assigned	Reader	Classification	Assigned	Reader	Classification
1	a	b	Incorrect	c	c	Correct	b	a	Incorrect
2	a	c	Incorrect	b	b	Correct	c	a	Incorrect
3	c	a	Incorrect	a	-	No decision	b	-	No decision
4	a	-	No decision	b	-	No decision	c	-	No decision
5	b	b	Correct	c	c	Correct	a	a	Correct
6	c	c	Correct	b	b	Correct	a	a	Correct
7	c	a	Incorrect	b	-	No decision	a	-	No decision
8	b	-	No decision	c	-	No decision	a	a	Correct
9	a	-	No decision	c	-	No decision	b	-	No decision
10	c	-	No decision	a	c	Incorrect	b	-	No decision
11	b	-	No decision	c	-	No decision	a	-	No decision
12	b	-	No decision	a	-	No decision	c	c	Correct

Classification Accuracy

Correct Answers			Incorrect Answers			No Decision			
A	B	C	A	B	C	A-B	A-C	B-C	A-B-C
16.7%	33.3%	33.3%	33.3%	8.3%	16.7%	16.7%	8.3%	16.7%	25%
(2/12)	(4/12)	(4/12)	(4/12)	(1/12)	(2/12)	(2/12)	(1/12)	(2/12)	(3/12)
Total	27.8% (10/36)		Total	19.4% (7/36)		Total	52.8% (19/36)		

Supplementary Table 4
Results of the VOI-based analysis of the agreement of CT-free frameworks with the reference

Framework	μ -Maps									
	Difference (10^{-3} cm^{-1})					Relative Difference (%)				
	Mean	SD	Median	Q1	Q3	Mean	SD	Median	Q1	Q3
LSO-Tx	8.9	12.8	6.2	-0.5	15.1	18.4	38.9	6.4	-0.5	16.7
LSO-Tx w/ MLAA	1.2	12.6	-1.0	-5.8	5.0	3.4	27.9	-1.0	-5.7	5.1
LSO-Tx w/ MLACF	2.6	8.9	1.1	-4.9	6.6	3.5	11.1	1.1	-5.9	8.2
CNN	0	4.3	-0.3	-0.3	0.3	0.8	9.3	-0.3	-1.0	0.3
CNN w/ MLAA	-4.7	9.7	-3.3	-3.3	1.5	-9.9	24.8	-3.3	-10.7	1.6
CNN w/ MLACF	-1.4	10.2	-1.7	-1.7	2.0	-1.7	11.7	-2.0	-8.7	2.1

Supplementary Table 5

Differences in SUV_{mean} of CT-free frameworks with the CT-based reference based on VOI-analysis

All VOIs		Overall (n = 147)							Short-interval protocol (n = 58)							Long-interval protocol (n = 89)						
Framework		Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS
LSO-Tx		1.1	1.6	0.5	0.1	1.1	<0.001	1.94	0.4	0.6	0.2	0.1	0.5	<0.001	0.72	1.5	1.9	0.6	0.2	1.5	<0.001	2.40
LSO-Tx w/ MLAA		0.6	3.2	0.0	-0.3	0.1	0.319	3.26	-0.5	1.0	-0.1	-0.3	0.0	<0.001	1.08	1.3	3.9	0.1	-0.1	0.8	0.016	4.12
LSO-Tx w/ MLACF		0.5	1.0	0.2	0.1	0.6	<0.001	1.12	0.2	0.4	0.1	0.1	0.3	<0.001	0.45	0.7	1.2	0.4	0.1	0.8	<0.001	1.41
CNN		-0.4	0.7	-0.1	-0.3	-0.1	<0.001	0.81	-0.3	0.4	-0.1	-0.2	0.0	<0.001	0.44	-0.5	0.9	-0.2	-0.3	-0.1	<0.001	1.01
CNN w/ MLAA		-0.7	1.3	-0.1	-0.5	0.0	<0.001	1.48	-0.5	1.0	-0.1	-0.3	0.0	<0.001	1.10	-0.9	1.4	-0.2	-0.5	0.0	<0.001	1.64
CNN w/ MLACF		-0.2	0.6	0.0	-0.1	0.0	<0.001	0.63	-0.1	0.3	0.0	-0.1	0.1	0.153	0.36	-0.3	0.7	0.0	-0.2	0.0	<0.001	0.76
Healthy organs		Overall (n = 120)							Short-interval protocol (n = 50)							Long-interval protocol (n = 70)						
Framework		Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS
LSO-Tx		0.9	1.4	1.6	0.3	2.5	<0.001	1.66	0.4	0.6	0.3	0.1	0.9	<0.001	0.71	1.2	1.6	2.4	1.3	3.3	<0.001	2.05
LSO-Tx w/ MLAA		0.3	2.0	-0.5	-0.8	0.7	0.463	2.02	-0.5	1.0	-0.7	-0.7	-0.3	<0.001	1.14	0.9	2.3	-0.1	-0.8	1.9	0.008	2.49
LSO-Tx w/ MLACF		0.5	0.9	0.2	-0.3	1.0	<0.001	1.03	0.3	0.4	-0.4	-0.4	0.1	<0.001	0.46	0.7	1.2	0.5	0.1	2.0	<0.001	1.33
CNN		-0.2	0.3	-0.8	-1.6	-0.3	<0.001	0.36	-0.2	0.3	-0.3	-0.8	-0.3	<0.001	0.35	-0.3	0.4	-0.9	-1.8	-0.7	<0.001	0.45
CNN w/ MLAA		-0.6	1.2	-1.0	-1.9	-0.6	<0.001	1.34	-0.5	1.1	-0.5	-0.7	-0.2	<0.001	1.15	-0.6	1.3	-1.3	-1.9	-0.9	<0.001	1.46
CNN w/ MLACF		-0.1	0.4	-0.5	-0.8	-0.1	0.013	0.41	-0.1	0.3	-0.3	-0.6	-0.2	0.796	0.35	-0.2	0.4	-0.5	-1.2	0.0	0.004	0.42
Lesions		Overall (n = 27)							Short-interval protocol (n = 8)							Long-interval protocol (n = 19)						
Framework		Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS
LSO-Tx		2.0	2.1	0.5	0.1	1.5	<0.001	2.90	0.5	0.6	0.2	0.1	0.5	0.055	0.75	2.6	2.2	0.8	0.3	2.3	<0.001	3.41
LSO-Tx w/ MLAA		1.9	6.0	0.0	-0.4	0.2	0.696	6.29	-0.6	0.3	-0.2	-0.4	0.0	0.016	0.66	2.9	7.0	0.1	-0.2	0.9	0.541	7.53
LSO-Tx w/ MLACF		0.6	1.3	0.2	0.0	0.6	0.062	1.43	-0.1	0.4	0.1	0.0	0.3	0.383	0.43	0.8	1.4	0.4	0.1	0.9	0.014	1.66
CNN		-1.2	1.3	-0.2	-0.4	-0.1	<0.001	1.77	-0.6	0.5	-0.1	-0.2	0.0	0.008	0.77	-1.5	1.4	-0.2	-0.6	-0.1	<0.001	2.02
CNN w/ MLAA		-1.4	1.2	-0.2	-0.9	0.0	<0.001	1.84	-0.6	0.5	-0.2	-0.4	0.0	0.023	0.72	-1.8	1.3	-0.3	-1.0	-0.1	<0.001	2.18
CNN w/ MLACF		-0.6	1.0	0.0	-0.3	0.0	0.001	1.17	-0.3	0.3	0.0	-0.1	0.1	0.023	0.44	-0.8	1.2	-0.1	-0.4	0.0	0.014	1.42
Brain grey matter		Overall (n = 12)							Short-interval protocol (n = 5)							Long-interval protocol (n = 7)						
Framework		Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS
LSO-Tx		3.5	2.6	2.9	1.6	4.2	<0.001	4.36	1.7	0.8	1.5	1.4	2.1	0.063	1.90	4.8	2.6	4.1	3.1	5.6	0.016	5.43
LSO-Tx w/ MLAA		-1.5	3.1	-1.9	-3.5	-0.5	0.034	3.44	-2.8	2.0	-3.3	-4.7	-1.2	0.063	3.44	-0.5	3.4	-1.9	-2.0	-0.4	0.297	3.48
LSO-Tx w/ MLACF		2.2	2.0	1.7	0.9	2.4	0.001	2.97	0.9	0.7	0.8	0.4	1.4	0.125	1.13	3.1	2.2	2.3	1.7	3.9	0.016	3.76
CNN		-1.0	0.5	-0.9	-1.2	-0.8	0.001	1.12	-1.0	0.3	-0.9	-0.9	-0.8	0.063	1.04	-1.0	0.7	-1.0	-1.3	-0.7	0.031	1.18
CNN w/ MLAA		-3.8	1.2	-4.3	-4.8	-2.8	<0.001	3.98	-3.2	1.4	-2.6	-4.4	-2.3	0.063	3.50	-4.3	0.9	-4.5	-5.0	-3.7	0.016	4.38
CNN w/ MLACF		-1.0	0.6	-1.0	-1.4	-0.7	0.001	1.17	-1.0	0.4	-1.0	-1.2	-0.7	0.063	1.05	-0.9	0.7	-0.9	-1.5	-0.8	0.031	1.17
Brain white matter		Overall (n = 12)							Short-interval protocol (n = 5)							Long-interval protocol (n = 7)						
Framework		Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS
LSO-Tx		1.2	0.8	0.9	0.7	1.6	<0.001	1.44	0.7	0.4	0.6	0.5	0.7	0.063	0.86	1.5	0.8	1.1	0.9	2.0	0.016	1.71
LSO-Tx w/ MLAA		0.0	1.7	-0.5	-0.9	0.0	0.110	1.70	-0.7	0.5	-0.9	-1.0	-0.3	0.125	0.86	0.4	2.0	-0.4	-0.5	0.1	0.578	2.05
LSO-Tx w/ MLACF		0.7	0.6	0.6	0.4	1.0	<0.001	0.92	0.4	0.4	0.2	0.1	0.6	0.063	0.52	1.0	0.6	0.9	0.5	1.3	0.016	1.13
CNN		-0.2	0.1	-0.2	-0.2	-0.2	0.001	0.22	-0.2	0.1	-0.2	-0.3	-0.2	0.063	0.23	-0.2	0.2	-0.2	-0.2	-0.2	0.031	0.29
CNN w/ MLAA		-1.0	0.3	-1.0	-1.1	-0.8	<0.001	1.04	-0.8	0.3	-0.9	-1.0	-0.6	0.063	0.90	-1.1	0.3	-1.0	-1.2	-0.9	0.016	1.10
CNN w/ MLACF		-0.2	0.1	-0.2	-0.2	-0.1	0.005	0.22	-0.2	0.1	-0.1	-0.2	-0.1	0.063	0.19	-0.1	0.1	-0.2	-0.2	-0.1	0.047	0.20

Supplementary Table 6

Relative differences (%) in SUV_{mean} of CT-free frameworks with the CT-based reference based on VOI-analysis

All VOIs		Overall (n = 147)							Short-interval protocol (n = 58)							Long-interval protocol (n = 89)						
Framework		Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS
LSO-Tx		28.9	28.6	20.7	11.8	40.3	<0.001	40.7	16.5	15.1	15.7	5.3	21.8	<0.001	22.4	37.0	32.2	25.9	17.4	56.7	<0.001	49.1
LSO-Tx w/ MLAA		26.4	99.5	-3.0	-13.9	9.4	0.319	102.9	-12.4	11.5	-13.0	-17.9	-3.4	<0.001	17.0	51.7	121.0	3.7	-6.3	45.2	0.016	131.6
LSO-Tx w/ MLACF		14.6	15.3	12.9	3.9	22.0	<0.001	21.1	11.0	11.9	9.3	3.4	16.1	<0.001	16.2	16.9	16.7	15.5	4.8	25.5	<0.001	23.7
CNN		-8.9	7.0	-8.2	-11.1	-5.3	<0.001	11.3	-7.5	5.5	-7.0	-9.3	-5.3	<0.001	9.3	-9.9	7.7	-9.5	-12.4	-5.3	<0.001	12.5
CNN w/ MLAA		-12.3	13.3	-11.2	-20.0	-3.1	<0.001	18.1	-11.5	12.5	-10.6	-16.3	-2.3	<0.001	17.0	-12.8	13.8	-12.6	-22.1	-3.3	<0.001	18.9
CNN w/ MLACF		-1.6	10.2	-2.6	-7.3	3.4	<0.001	10.3	0.3	8.5	-1.5	-4.3	4.7	0.153	8.5	-2.8	11.0	-3.3	-8.3	1.6	<0.001	11.3
Healthy organs		Overall (n = 120)							Short-interval protocol (n = 50)							Long-interval protocol (n = 70)						
Framework		Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS
LSO-Tx		30.1	29.8	20.9	12.3	44.7	<0.001	42.4	17.3	15.5	15.7	7.3	21.8	<0.001	23.2	39.3	33.9	24.9	17.7	57.0	<0.001	51.9
LSO-Tx w/ MLAA		27.5	104.7	-2.0	-14.3	8.6	0.463	108.3	-12.6	12.1	-13.0	-18.1	-2.5	<0.001	17.5	56.2	129.3	4.5	-4.5	54.6	0.008	141.0
LSO-Tx w/ MLACF		16.5	14.7	14.1	7.0	23.8	<0.001	22.1	13.0	11.2	10.8	4.3	16.8	<0.001	17.1	19.1	16.4	17.4	8.4	26.7	<0.001	25.1
CNN		-7.6	4.5	-8.1	-10.8	-5.2	<0.001	8.8	-6.7	3.8	-6.9	-8.6	-5.3	<0.001	7.7	-8.3	4.8	-8.9	-12.0	-5.2	<0.001	9.6
CNN w/ MLAA		-11.3	13.7	-10.4	-19.9	-2.1	<0.001	17.8	-11.5	12.8	-10.4	-16.3	-2.3	<0.001	17.2	-11.1	14.3	-10.2	-21.9	-2.2	<0.001	18.1
CNN w/ MLACF		-0.3	9.2	-1.6	-5.7	3.9	0.013	9.2	1.5	8.3	0.5	-3.7	5.8	0.796	8.5	-1.6	9.6	-2.8	-6.8	2.7	0.004	9.7
Lesions		Overall (n = 27)							Short-interval protocol (n = 8)							Long-interval protocol (n = 19)						
Framework		Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS
LSO-Tx		23.5	21.6	20.7	8.0	30.1	<0.001	31.9	11.6	11.0	10.7	1.5	21.6	0.055	16.0	28.5	23.0	26.0	15.1	40.2	<0.001	36.6
LSO-Tx w/ MLAA		21.3	71.6	-6.0	-13.2	8.6	0.696	74.7	-11.2	7.1	-11.9	-14.9	-8.1	0.016	13.3	35.0	81.5	-3.0	-11.1	31.2	0.541	88.7
LSO-Tx w/ MLACF		5.8	14.4	3.5	-4.1	13.6	0.062	15.5	-1.3	8.6	-5.8	-7.2	5.7	0.383	8.7	8.8	15.3	4.8	1.5	16.9	0.014	17.6
CNN		-14.7	11.7	-10.4	-16.8	-7.0	<0.001	18.8	-12.1	10.2	-9.1	-11.3	-5.9	0.008	15.9	-15.7	12.1	-11.4	-20.9	-8.6	<0.001	19.9
CNN w/ MLAA		-16.8	10.3	-13.6	-20.4	-10.7	<0.001	19.7	-11.6	10.1	-10.7	-13.8	-7.1	0.023	15.4	-19.0	9.6	-16.1	-21.8	-11.7	<0.001	21.3
CNN w/ MLACF		-7.0	12.3	-8.7	-12.5	-2.1	0.001	14.2	-7.0	5.2	-8.8	-10.9	-2.9	0.023	8.7	-7.0	14.3	-8.7	-13.5	-0.7	0.014	15.9
Brain grey matter		Overall (n = 12)							Short-interval protocol (n = 5)							Long-interval protocol (n = 7)						
Framework		Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS
LSO-Tx		26.7	14.3	23.3	16.6	32.6	<0.001	30.3	16.1	6.5	15.4	11.8	17.0	0.063	17.4	34.2	13.5	28.5	23.3	46.6	0.016	36.8
LSO-Tx w/ MLAA		-14.6	21.4	-15.5	-28.3	-3.8	0.034	25.9	-25.1	16.0	-26.0	-41.1	-15.3	0.063	29.8	-7.0	21.6	-12.5	-17.3	-3.0	0.297	22.7
LSO-Tx w/ MLACF		16.0	12.0	14.0	8.3	21.5	0.001	20.0	7.9	6.1	8.8	3.0	12.9	0.125	10.0	21.9	11.7	20.8	12.5	31.0	0.016	24.8
CNN		-8.3	4.0	-9.3	-11.1	-6.0	0.001	9.2	-9.6	2.4	-9.2	-11.1	-8.3	0.063	9.9	-7.4	4.6	-9.5	-10.7	-5.2	0.031	8.7
CNN w/ MLAA		-31.6	7.9	-32.1	-38.0	-28.7	<0.001	32.6	-30.5	11.0	-34.4	-40.3	-18.4	0.063	32.4	-32.5	4.1	-30.7	-35.6	-29.2	0.016	32.7
CNN w/ MLACF		-8.1	4.6	-8.1	-11.0	-7.4	0.001	9.3	-9.7	4.0	-9.9	-13.6	-8.0	0.063	10.5	-7.0	4.7	-7.9	-9.6	-7.3	0.031	8.5
Brain white matter		Overall (n = 12)							Short-interval protocol (n = 5)							Long-interval protocol (n = 7)						
Framework		Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS
LSO-Tx		34.0	15.8	27.6	23.8	45.7	<0.001	37.5	24.4	11.4	22.8	13.8	27.1	0.063	26.9	40.8	15.0	38.4	26.6	52.8	0.016	43.5
LSO-Tx w/ MLAA		-5.3	39.1	-11.6	-27.4	0.3	0.110	39.5	-22.6	15.7	-25.4	-38.9	-10.2	0.125	27.5	7.0	45.6	-10.7	-13.0	1.8	0.578	46.1
LSO-Tx w/ MLACF		20.5	12.7	21.3	11.7	29.2	<0.001	24.1	12.6	10.8	7.0	3.3	22.9	0.063	16.6	26.2	10.7	21.4	17.7	35.2	0.016	28.3
CNN		-6.9	3.8	-7.3	-8.5	-5.6	0.001	7.9	-8.0	2.2	-8.2	-9.3	-7.0	0.063	8.3	-6.1	4.4	-6.9	-7.6	-5.6	0.031	7.5
CNN w/ MLAA		-29.0	7.9	-29.5	-36.6	-24.1	<0.001	30.1	-28.1	10.7	-32.5	-37.9	-16.2	0.063	30.1	-29.7	4.9	-28.9	-33.3	-25.9	0.016	30.1
CNN w/ MLACF		-5.0	3.5	-5.5	-6.4	-3.7	0.005	6.1	-6.2	3.2	-4.3	-9.1	-4.0	0.063	7.0	-4.1	3.4	-5.6	-6.0	-3.8	0.047	5.3

Supplementary Table 7
SUV_{mean} differences estimated for different PET imaging frameworks over different VOI-types

VOI	<i>n</i>	CNN - CT				CNN with MLACF – CT				CNN with MLACF – CNN			
		Mean (%)	SD (%)	<i>P</i> -value	RSS	Mean (%)	SD (%)	<i>P</i> -value	RSS	Mean (%)	SD (%)	<i>P</i> -value	RSS
Adipose	12	-7.24	4.75	0.001	8.66	6.18	13.4	0.266	14.8	14.2	10.9	0.002	14.2
Asc. aorta	12	-8.78	5.79	0.002	10.5	4.19	7.09	0.092	8.24	14.4	7.03	0.000	14.4
Bone marrow	12	-7.82	5.07	0.001	9.32	-4.24	6.73	0.077	7.95	4.11	8.33	0.233	4.11
Grey matter	12	-8.29	3.96	0.001	9.19	-8.15	4.61	0.001	9.36	0.20	3.83	0.677	0.2
White matter	12	-6.87	3.76	0.001	7.83	-4.98	3.50	0.005	6.09	2.07	2.56	0.012	2.07
Kidney	12	-6.24	3.61	0.000	7.21	-2.26	5.90	0.009	6.32	2.16	5.75	0.380	2.16
Liver	12	-8.38	3.91	0.000	9.25	-0.73	7.45	0.677	7.49	8.22	4.96	0.003	8.22
Lung	12	-7.47	5.55	0.002	9.31	2.99	6.17	0.129	6.86	11.5	7.09	0.000	11.5
Muscle	12	-7.47	3.53	0.000	8.26	4.78	12.8	0.424	13.7	13.5	15.9	0.000	13.5
Spleen	12	-7.69	3.53	0.000	8.46	0.83	6.19	0.301	6.25	9.19	4.50	0.001	9.19
Lesions	27	-14.7	11.7	0.000	18.8	-6.98	12.3	0.001	14.1	10.1	14.6	0.000	10.1

Supplementary Table 8

Coefficients of variation and lesion contrast-to-noise values and their difference from CT-based reference

(n = 12)																			
Framework	CV in μ -maps					CV difference in μ -maps							Relative CV difference in μ -maps						
	Mean	SD	Median	Q1	Q3	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS
CT	0.3	0.1	0.3	0.2	0.3	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LSO-Tx	4.8	2.4	3.9	3.2	5.1	4.5	2.4	3.5	3.0	4.9	<0.001	5.12	1758	1236	1104	970	2253	<0.001	2149
LSO-Tx w/ MLAA	3.5	0.6	3.3	3.2	3.6	3.2	0.6	3.0	2.9	3.2	<0.001	3.22	1181	418	1056	946	1312	<0.001	1253
LSO-Tx w/ MLACF	3.8	0.9	3.7	3.4	4.2	3.5	0.9	3.4	3.0	3.7	<0.001	3.6	1303	576	1231	910	1478	<0.001	1425
CNN	0.2	0.1	0.2	0.2	0.2	-0.1	0.1	-0.1	-0.1	0.0	0.007	0.13	-27	25	-33	-41	-8	0.005	37
CNN w/ MLAA	3.0	0.4	3.0	2.7	3.2	2.7	0.4	2.6	2.5	2.9	<0.001	2.69	986	291	1007	730	1143	<0.001	1028
CNN w/ MLACF	4.1	0.8	3.9	3.6	4.4	3.8	0.8	3.7	3.3	4.1	<0.001	3.84	1399	539	1319	1003	1570	<0.001	1499

(n = 12)																			
Framework	CV in AC-PET					CV difference in AC-PET							Relative CV difference in AC-PET						
	Mean	SD	Median	Q1	Q3	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS
CT	7.4	0.8	7.5	6.8	7.9	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LSO-Tx	7.8	0.9	7.8	7.5	8.2	0.5	0.8	0.2	0.0	0.6	0.077	0.95	7.0	12.7	2.9	-0.2	7.6	0.092	14.4
LSO-Tx w/ MLAA	6.9	1.2	7.1	6.4	7.6	-0.5	1.4	-0.1	-0.3	0.4	0.910	1.49	-5.2	17.3	-0.8	-3.7	6.0	0.910	18.1
LSO-Tx w/ MLACF	6.8	1.1	7.0	6.4	7.6	-0.6	1.4	0.0	-0.3	0.1	0.791	1.49	-7.0	16.6	0.1	-4.1	1.9	0.791	18.0
CNN	6.8	1.1	6.9	6.3	7.6	-0.6	1.3	0.0	-0.3	0.1	0.339	1.42	-7.1	15.6	-0.5	-3.1	0.8	0.380	17.1
CNN w/ MLAA	6.8	1.0	7.0	6.4	7.6	-0.6	1.3	-0.1	-0.4	0.1	0.301	1.38	-6.7	15.3	-0.6	-4.8	1.0	0.339	16.7
CNN w/ MLACF	6.8	1.1	7.1	6.4	7.7	-0.5	1.4	0.1	-0.2	0.2	0.970	1.46	-6.0	16.6	1.5	-2.8	3.2	0.970	17.6

(n = 27)																			
Framework	Lesion CNR in AC-PET					Lesion CNR difference in AC-PET							Relative lesion CNR difference in AC-PET						
	Mean	SD	Median	Q1	Q3	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS
CT	3.2	0.8	2.9	2.7	3.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LSO-Tx	3.1	0.7	2.9	2.6	3.8	-0.1	0.1	-0.1	-0.1	0.0	0.017	0.13	-1.9	4.1	-1.8	-3.9	0.4	0.030	4.5
LSO-Tx w/ MLAA	3.0	0.6	2.9	2.5	3.4	-0.2	0.4	-0.1	-0.2	0.0	<0.001	0.4	-5.4	8.0	-1.4	-6.9	-0.4	<0.001	9.6
LSO-Tx w/ MLACF	3.0	0.6	2.8	2.5	3.4	-0.2	0.3	-0.1	-0.2	0.0	<0.001	0.39	-5.0	7.8	-2.2	-5.0	-0.2	<0.001	9.3
CNN	3.0	0.7	3.0	2.5	3.5	-0.2	0.4	0.0	-0.2	0.0	0.106	0.4	-4.7	9.1	-0.3	-5.1	0.5	0.086	10.3
CNN w/ MLAA	3.0	0.7	2.9	2.6	3.4	-0.2	0.4	-0.1	-0.2	0.0	<0.001	0.4	-5.5	8.4	-1.5	-5.0	-0.5	<0.001	10.0
CNN w/ MLACF	3.0	0.6	2.9	2.5	3.4	-0.2	0.3	0.0	-0.2	0.0	<0.001	0.39	-4.9	7.7	-1.6	-5.8	-0.5	<0.001	9.1

Supplementary Table 9

Relative differences (%) in SUV_{mean} between the CT-based reference and the CT-free frameworks with substituted low-attenuating objects

All VOIs		Overall (n = 147)							Short-interval protocol (n = 58)							Long-interval protocol (n = 89)						
Framework	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS	
LSO-Tx [†]	30.4	25.6	24.5	13.6	39.8	<0.001	39.7	20.8	13.7	18.7	10.8	26.3	<0.001	24.9	36.2	29.2	29.9	17.2	53.8	<0.001	46.5	
LSO-Tx w/ MLAA [†]	25.9	65.7	6.8	-5.1	25.4	<0.001	70.6	-2.7	11.4	-2.8	-8.7	6.1	0.033	11.7	43.3	77.9	14.1	0.4	49.3	<0.001	89.1	
LSO-Tx w/ MLACF [†]	18.7	14.5	17.2	8.5	26.0	<0.001	23.7	14.2	11.8	15.3	5.2	19.1	<0.001	18.4	21.4	15.4	21.5	9.6	28.3	<0.001	26.3	
CNN [†]	-3.0	7.4	-1.6	-4.2	0.7	<0.001	8.0	-1.2	6.2	-0.4	-2.0	0.9	0.031	6.3	-4.2	7.8	-2.6	-6.7	0.6	<0.001	8.9	
CNN w/ MLAA [†]	-5.6	13.5	-4.19	-13.5	3.0	<0.001	14.6	-5.3	13.0	-3.6	-11.6	4.3	0.009	14.0	-5.8	13.9	-5.2	-14.6	2.7	<0.001	15.0	
CNN w/ MLACF [†]	4.9	10.9	4.0	-0.7	9.1	<0.001	12.0	6.2	8.6	4.7	0.2	11.8	<0.001	10.6	4.1	12.1	3.4	-1.9	8.3	0.003	12.8	

Healthy organs		Overall (n = 120)							Short-interval protocol (n = 50)							Long-interval protocol (n = 70)						
Framework	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS	
LSO-Tx [†]	32.2	25.9	25.4	14.9	43.5	<0.001	41.4	21.5	14.1	19.1	11.9	27.7	<0.001	25.7	39.2	29.3	30.9	18.5	55.1	<0.001	49.0	
LSO-Tx w/ MLAA [†]	27.3	68.3	7.7	-4.6	26.2	<0.001	73.6	-2.4	11.7	-2.4	-8.7	6.5	0.113	11.9	46.6	81.7	14.5	1.3	56.5	<0.001	94.0	
LSO-Tx w/ MLACF [†]	20.5	14.1	18.9	11.4	27.5	<0.001	24.9	15.8	11.3	16.1	9.5	19.7	<0.001	19.4	23.6	14.9	22.7	13.9	28.8	<0.001	27.9	
CNN [†]	-1.9	5.2	-1.1	-3.6	0.9	<0.001	5.6	-0.6	5.1	-0.3	-1.6	1.2	0.110	5.1	-2.8	5.2	-2.3	-5.3	0.7	<0.001	5.9	
CNN w/ MLAA [†]	-4.6	13.7	-3.7	-13.3	4.4	<0.001	14.5	-5.2	13.3	-3.6	-11.6	4.3	0.028	14.3	-4.2	13.9	-3.7	-14.6	4.4	0.002	14.6	
CNN w/ MLACF [†]	6.1	9.9	4.7	0.1	10.1	<0.001	11.6	7.2	8.5	5.7	2.1	12.1	<0.001	11.1	5.3	10.7	4.5	-0.7	8.6	<0.001	12.0	

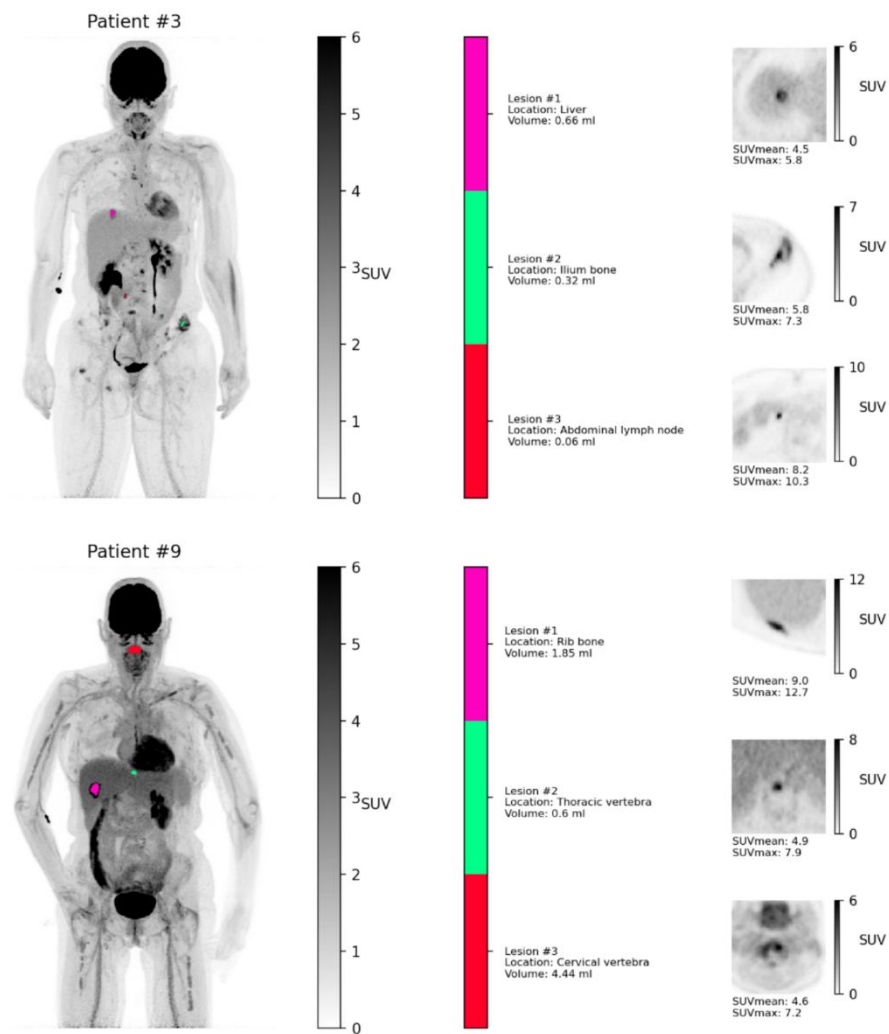
Lesions		Overall (n = 27)							Short-interval protocol (n = 8)							Long-interval protocol (n = 19)						
Framework	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS	
LSO-Tx [†]	20.1	20.9	21.7	5.6	29.4	<0.001	29.0	16.2	9.0	14.7	8.7	24.8	0.008	18.5	21.8	24.1	23.5	2.3	31.0	0.003	32.4	
LSO-Tx w/ MLAA [†]	18.2	48.1	2.1	-6.9	15.1	0.258	51.5	-5.1	8.7	-5.4	-9.7	-0.4	0.148	10.1	28.1	54.2	2.5	-4.0	32.2	0.055	61.0	
LSO-Tx w/ MLACF [†]	8.8	12.6	7.5	3.2	15.1	0.001	15.3	2.9	8.4	0.7	-2.0	10.8	0.844	8.9	11.3	13.2	8.4	7.1	19.2	0.003	17.3	
CNN [†]	-9.1	12.6	-3.8	-10.7	-1.0	<0.001	15.5	-5.2	10.6	-1.4	-4.2	-0.3	0.109	11.8	-10.7	13.0	-7.0	-16.0	-1.6	<0.001	16.9	
CNN w/ MLAA [†]	-10.8	11.4	-9.1	-14.8	-3.5	<0.001	15.6	-5.5	10.7	-4.1	-9.2	0.6	0.250	12.0	-13.0	10.9	-10.7	-17.6	-3.9	<0.001	16.9	
CNN w/ MLACF [†]	-1.5	13.7	-0.6	-8.1	3.7	0.313	13.7	-1.2	5.2	-1.5	-3.8	1.3	0.547	5.4	-1.6	15.9	-0.6	-9.4	3.7	0.352	16.0	

Brain grey matter		Overall (n = 12)							Short-interval protocol (n = 5)							Long-interval protocol (n = 7)						
Framework	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS	
LSO-Tx [†]	35.2	13.9	31.6	24.3	37.8	<0.001	37.8	25.8	5.2	24.1	23.8	30.2	0.063	26.3	41.9	14.3	33.5	31.6	53.0	0.016	44.2	
LSO-Tx w/ MLAA [†]	-6.4	17.7	-7.0	-12.7	7.8	0.339	18.8	-13.7	16.3	-8.0	-22.6	-6.0	0.188	21.3	-1.2	16.8	-4.7	-9.0	9.3	0.813	16.9	
LSO-Tx w/ MLACF [†]	25.0	13.6	21.3	17.0	30.8	<0.001	28.4	15.3	8.1	16.9	9.6	17.0	0.063	17.3	31.9	12.5	25.8	21.3	40.2	0.016	34.2	
CNN [†]	-0.8	1.5	-0.8	-1.7	-0.3	0.129	1.7	-1.4	1.0	-1.1	-1.6	-0.6	0.063	1.7	-0.3	1.7	-0.5	-1.8	0.5	0.688	1.8	
CNN w/ MLAA [†]	-25.3	8.5	-24.8	-33.9	-19.9	<0.001	26.7	-24.7	10.9	-27.3	-34.6	-15.2	0.063	27.0	-25.7	6.1	-22.2	-30.7	-20.8	0.016	26.5	
CNN w/ MLACF [†]	-0.5	5.0	0.4	-4.2	2.9	0.970	5.1	-2.6	4.2	-0.1	-4.1	0.4	0.625	4.9	1.0	5.1	2.3	-2.0	4.6	0.688	5.2	

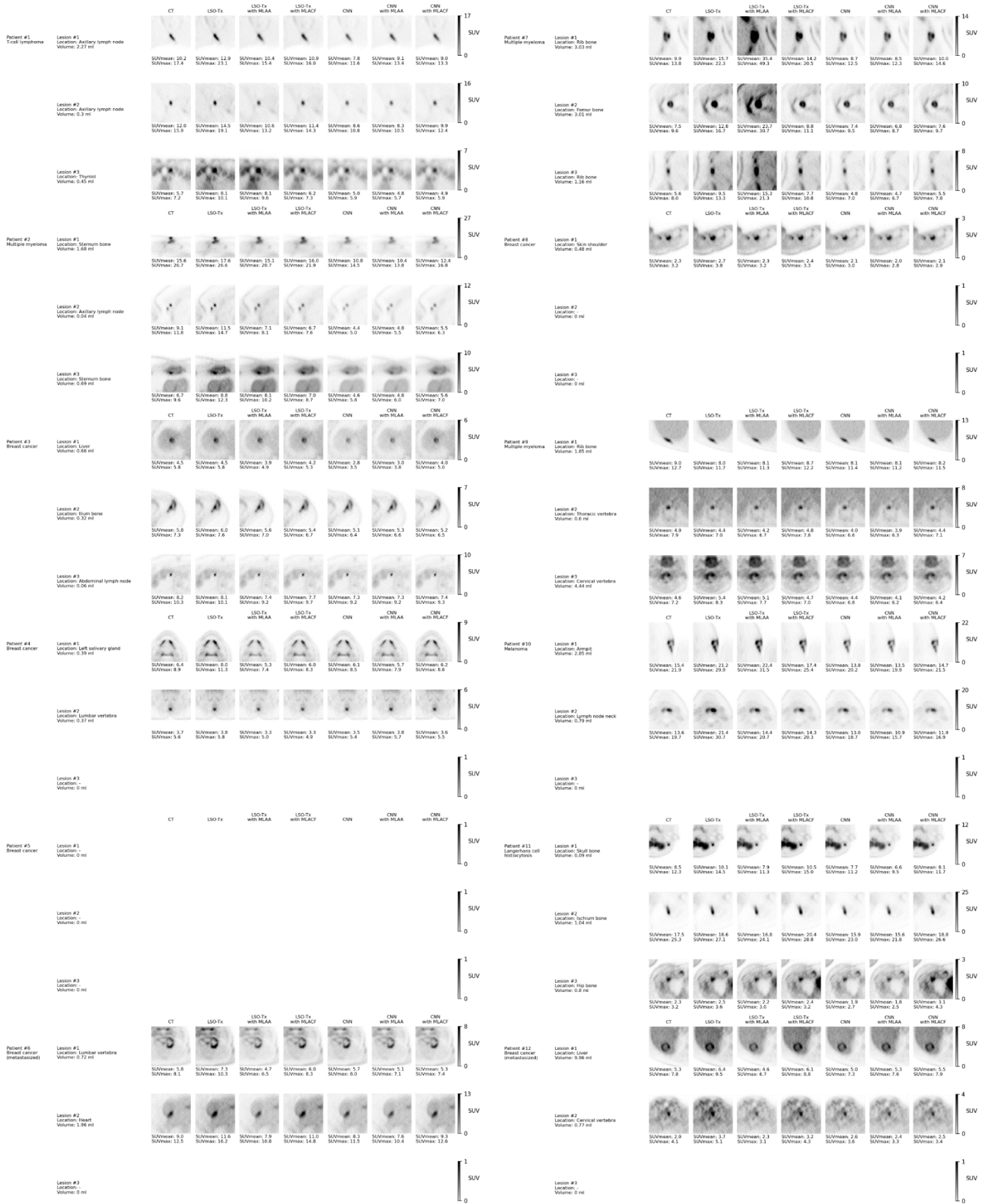
Brain white matter		Overall (n = 12)							Short-interval protocol (n = 5)							Long-interval protocol (n = 7)						
Framework	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS	Mean	SD	Median	Q1	Q3	P-value	RSS	
LSO-Tx [†]	43.0	16.8	40.1	33.0	51.4	<0.001	46.2	33.4	11.1	36.7	22.6	40.3	0.063	35.2	49.9	16.8	43.2	37.2	63.0	0.016	52.7	
LSO-Tx w/ MLAA [†]	1.0	30.5	-3.9	-11.6	9.7	0.622	30.6	-11.7	16.1	-6.5	-22.7	-1.4	0.313	19.9	10.2	34.9	0.1	-7.7	13.5	0.688	36.3	
LSO-Tx w/ MLACF [†]	29.1	15.1	26.5	21.2	36.7	<0.001	32.8	19.6	11.9	15.4	11.1	31.6	0.063	22.9	35.9	13.3	26.5	25.9	44.8	0.016	38.3	
CNN [†]	-0.3	2.8	-0.5	-2.8	2.2	0.733	2.8	-1.3	1.5	-0.9	-2.7	-0.1	0.188	1.9	0.4	3.3	2.0	-1.9	3.0	0.813	3.3	
CNN w/ MLAA [†]	-23.6	9.1	-23.3	-33.4	-17.0	<0.001	25.3	-23.4	11.4	-26.3	-34.6	-13.3	0.063	26.1	-23.8	7.0	-20.4	-29.9	-18.9	0.016	24.8	
CNN w/ MLACF [†]	2.1	4.4	1.5	-1.8	5.9	0.266	4.9	0.3	2.9	-0.9	-1.5	0.7	0.813	2.9	3.4	4.8	4.4	-0.4	6.8	0.219	5.9	

Supplementary Table 10						
Performance differences in % of SUV_{mean} between pure CT-free frameworks and their LAO-substituted counterparts. The average volume and μ -values of the						
<i>(n = 147)</i>						
Framework	Mean	SD	Median	Q1	Q3	<i>P</i> -value
LSO-Tx	1.8	8.8	4.0	-1.5	7.0	<0.001
LSO-Tx w/ MLAA	-1.1	37.9	6.8	4.5	9.2	<0.001
LSO-Tx w/ MLACF	4.4	5.0	4.3	1.0	7.9	<0.001
CNN	6.3	2.3	6.3	4.6	8.0	<0.001
CNN w/ MLAA	6.7	2.3	6.9	5.1	8.4	<0.001
CNN w/ MLACF	6.4	2.6	6.1	4.6	8.3	<0.001
Combined	4.1	16.3	5.9	3.5	8.3	0.000
Overview of low-attenuating objects	Volume (Liters)		μ -values (cm^{-1})			
	Mean	SD	Mean	SD		
	111.5	12.9	0.001349	0.000408		

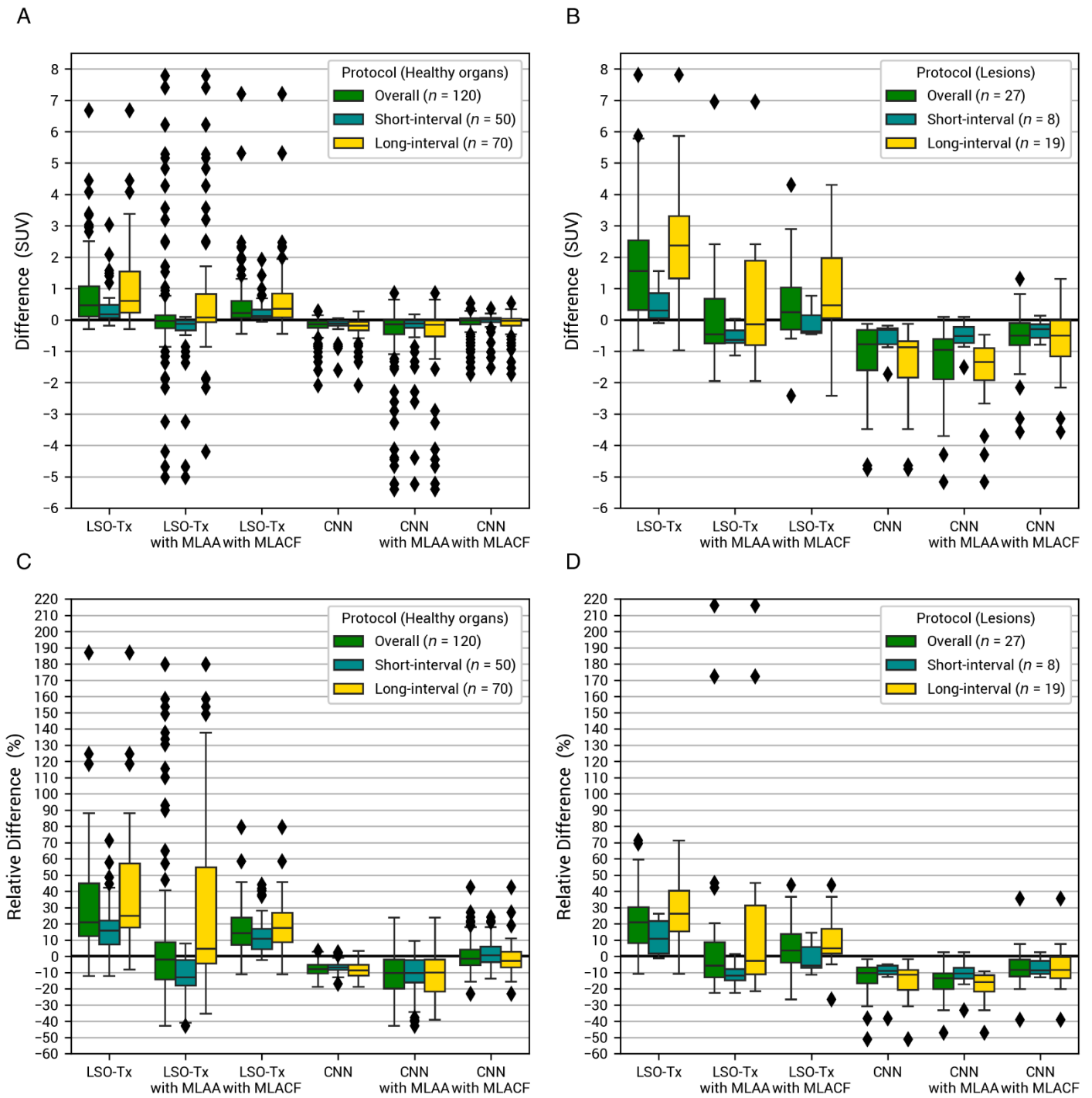
Supplementary Figures



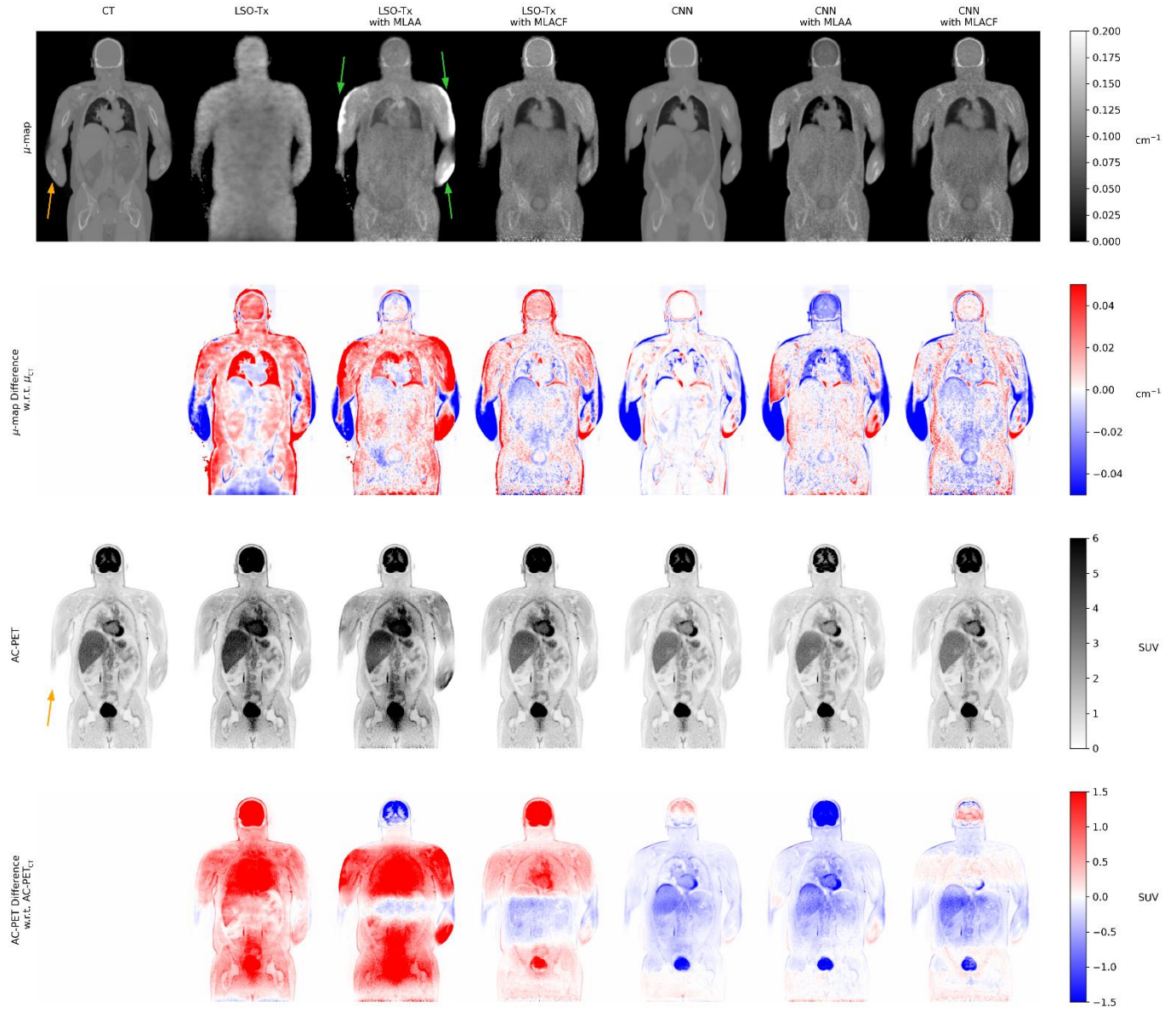
Supplementary Figure 1. Two patient examples of lesion VOIs overlaid onto a maximum-intensity projection of AC-PET_{CT} images. For each lesion, an additional axial slice of AC-PET_{CT} is presented, cropped and center at the lesion.



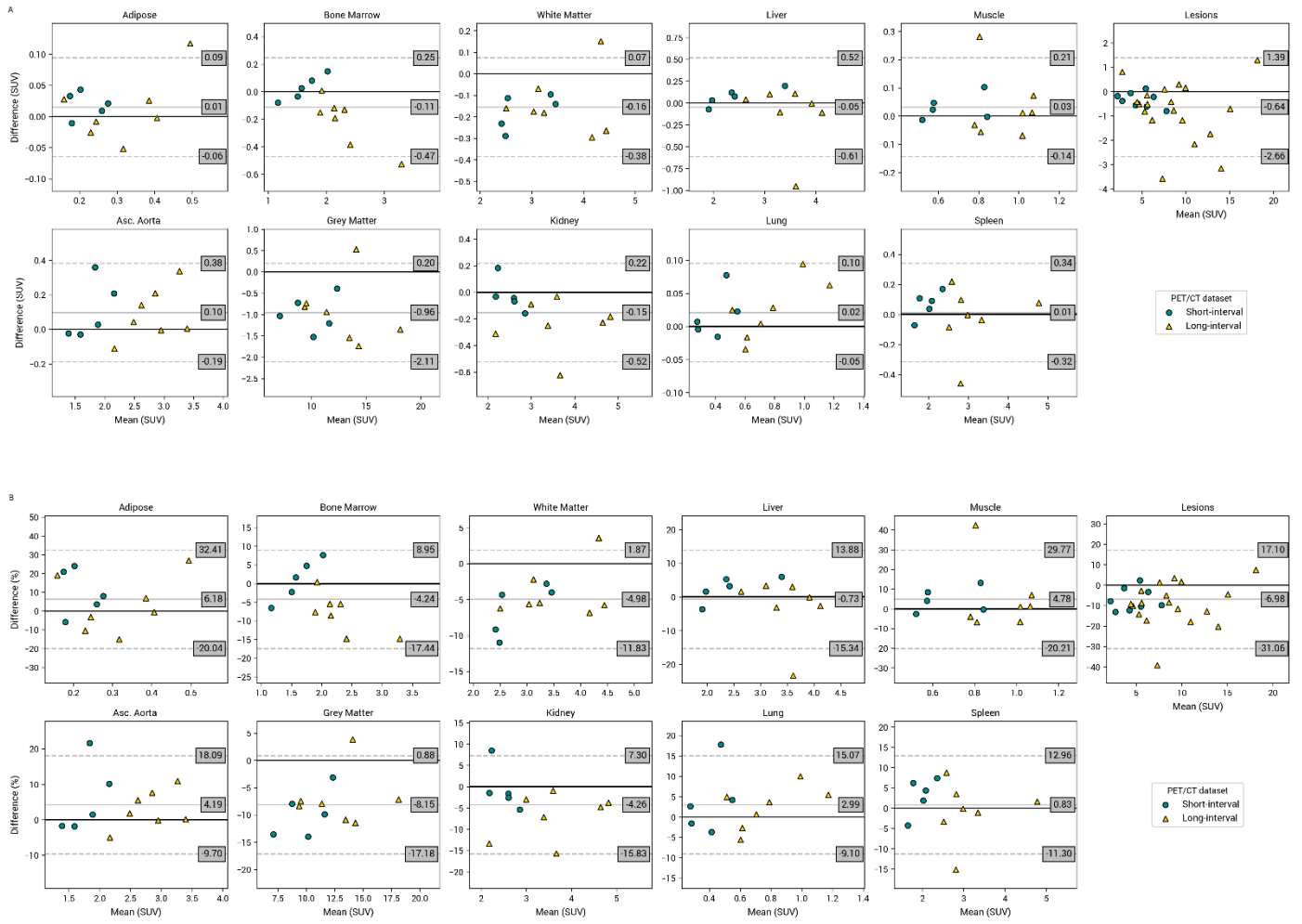
Supplementary Figure 2. Axial slices of all ^{18}F -FDG PET lesions used in the VOI analysis ($n = 27$), as generated by the reference CT-based and the investigated CT-free PET frameworks. The SUV_{mean} and SUV_{max} extracted using CT-based VOIs are also annotated.



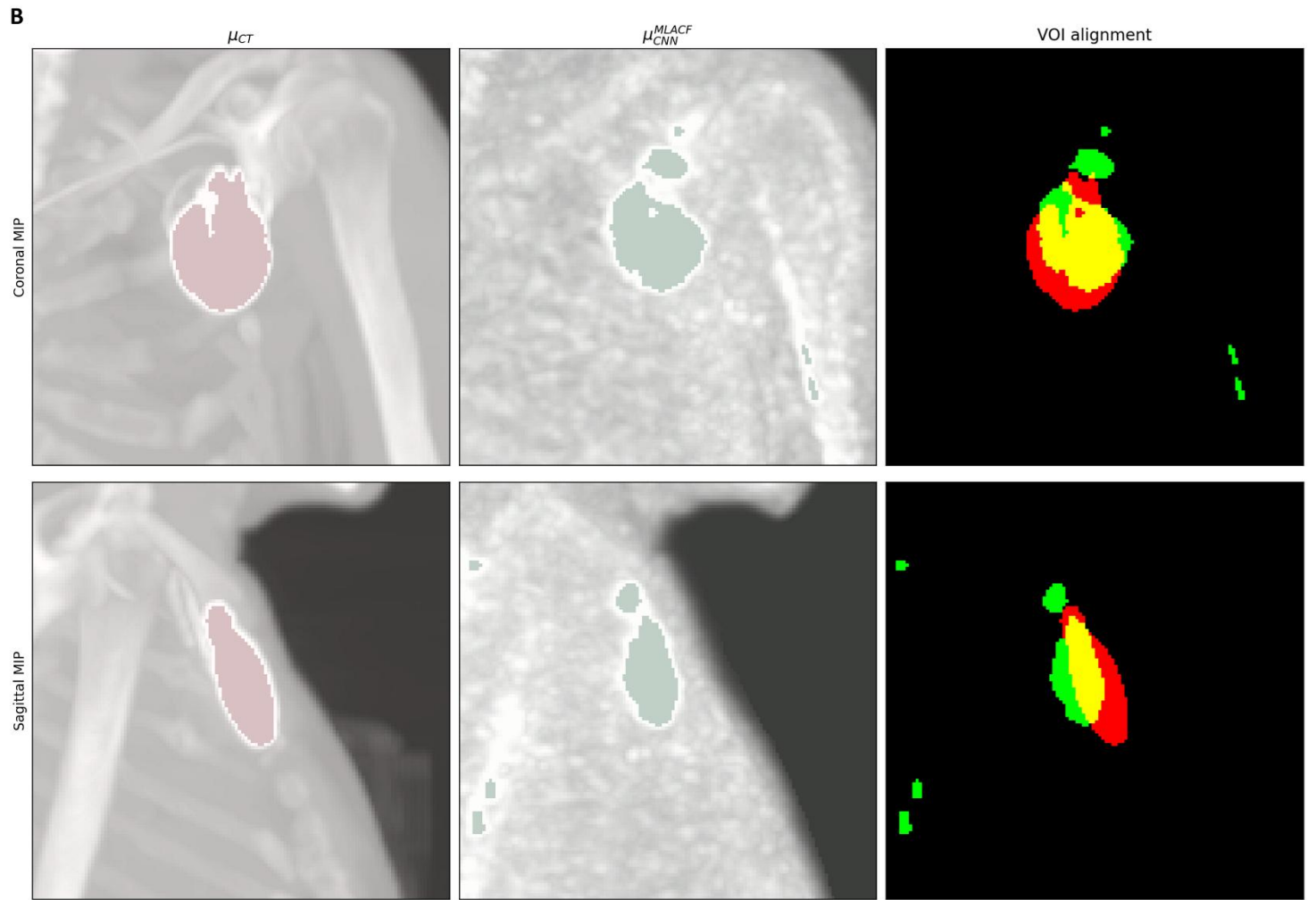
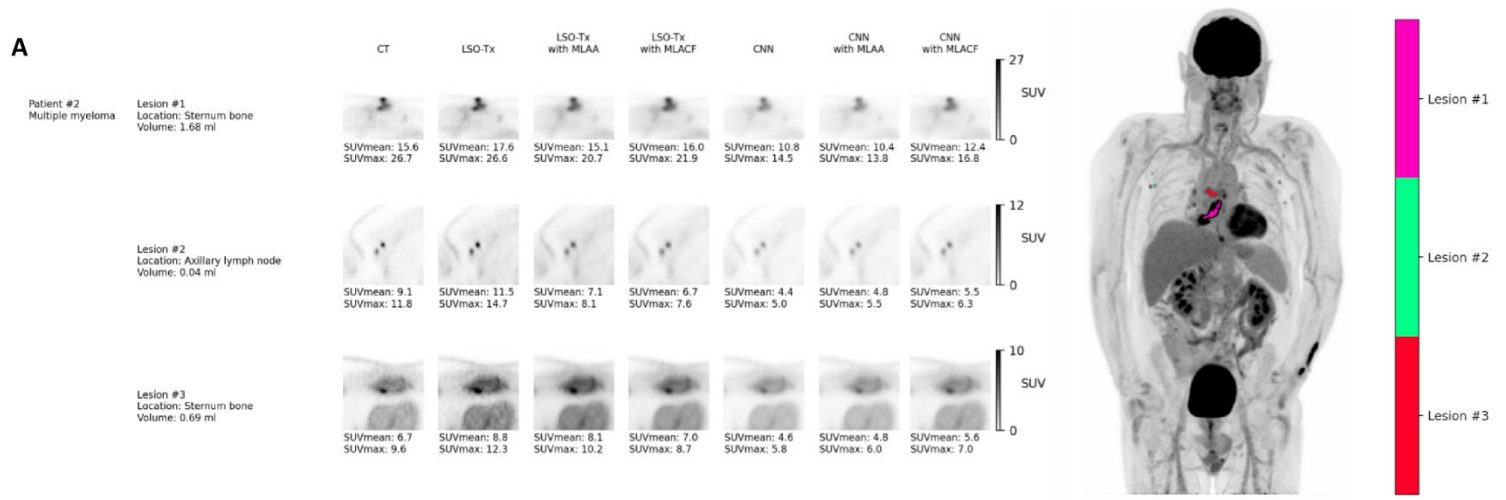
Supplementary Figure 3. Box-plots with whiskers of the differences (A, B) and relative differences (C, D) of SUVmean between the CT-based reference and each of the investigated CT-free frameworks. In (A) and (C) only healthy organ VOIs were used, while for (B) and (D) only lesion VOIs.



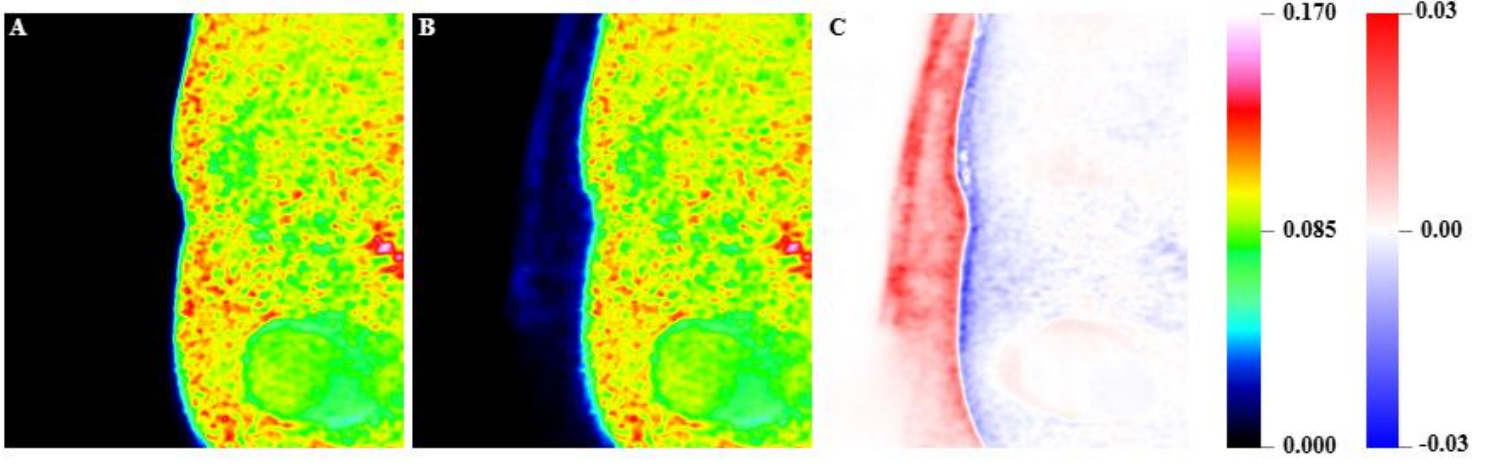
Supplementary Figure 4. Coronal slices of μ -maps and their equivalent AC-PET images as produced by the CT-based and the six CT-free frameworks of a patient (110 kg, 33 BMI) acquired using protocol C with long time-interval between LD-CT and PET. Annotated with the orange arrow, motion between μ_{CT} and AC-PET_{CT} can be observed at the right arm. None of the μ -maps generated with the CT-free frameworks exhibits the same mismatch. The green arrows point to locations where the MLAA-enhancement of μ_{LSO-Tx} occasionally produced severe hyper-intense artifacts, possibly due to arms extending the transaxial FoV.



Supplementary Figure 5. Bland-Altman plots to measure the SUV_{mean} agreement of the MLACF-enhanced CNN framework with the clinical PET/CT one based on the VOI-analysis. For each plot and each VOI, the x-axis value is calculated as the mean of SUVs of the measured method and the PET/CT one. The y-axis value is calculated as the difference of these two SUV values for A or their relative difference for B. The measurement bias for each method is calculated by taking the mean of y-axis values.



Supplementary Figure 6. The two largest lesion SUV_{mean} underestimations with CNN with MLACF occurred in the same long-interval patient (#2). In (A), all lesion VOIs of patient #2 are overlaid on the maximum intensity projection of the AC-PET_{CT} image, along with axial slices of AC-PET images as produced by all CT-free frameworks. One lesion was located superficially in the sternum (1.68 mL, -3.15 SUV bias), whereas the second was a small axillary lymph-node VOI of 0.04 mL (9 voxels, -3.57 SUV bias). The patient's PET-CT body-contour DSC was 0.963, lower than the 0.978 ± 0.006 observed in short-interval scans, with visible mismatch at the upper torso, shoulders, and arms. The specific patient also had a metallic cardiac pacemaker placed on the upper torso, with μ -values $>0.25 \text{ cm}^{-1}$ in μ_{CT} . As demonstrated in the coronal and sagittal MIPs of (B), this pacemaker was only partially reproduced in CNN with MLACF. A spatial mismatch between the pacemaker contours ($>0.25 \text{ cm}^{-1}$) of μ_{CT} (red) and μ_{CNN}^{MLACF} (green) was also observed. These observations indicate multiple potential contributors to the outliers. However, their individual effects could not be isolated.



Supplementary Figure 7. Sagittal slices of μ -maps (cm^{-1}) produced by MLACF using two different priors: the CT-free μ_{CNN} (A) and the CT-assisted with substituted LAOs $\mu_{\text{CNN}}^{\dagger}$ (B). In (C), the (B-A) difference-map is estimated that highlights the differences in final MLACF-convergence depending on the prior. While LAOs were not generated by $\mu_{\text{CNN}}^{\text{MLACF}}$, increased μ -values at the LAO-body interfaces were observed. Such observations suggest that MLACF with TOF, might partially compensate for the missed contributions in attenuation of LAOs by artificially elevating nearby μ -values.