Electronic Supplementary Material

Improving PET Quantification of Small Animal [^{68}Ga]DOTA-labeled PET/CT Studies by using a CT-based Positron Range Correction

Journal: Molecular Imaging and Biology

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Running title: Improved quantification of small animal ^{68}Ga-DOTA-labelled PET

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Cell culture, xenotransplantation and synthesis of [^{68}Ga]DOTA-peptides.

Pheochromocytoma PC12 and pancreatic acinar carcinoma ARJ42 cells were purchase from Sigma-Aldrich. CH-157MN meningioma tumor cells were provided by Randy Jensen, from the Department of Neurosurgery of the University of Utah Health Care. PC12 and AR42J were grown in Hanks F-12 culture medium supplemented with horse serum (15%), fetal calf serum (5%) and penicillin-streptomycin (1%). CH-157MN were grown in Dulbecco's Modified Eagle's Medium (DMEM) containing 10% fetal bovine serum, 2 mM L-glutamine, 50 units/ml penicillin, and 50 µg/ml streptomycin. Cultures were maintained at 37ºC and in 5% CO_2. Cell transplantation was performed subcutaneously in the right mouse flank with approximately 1.4-1.5 x 10^6 cells.

The precursors were obtained from BCN Peptides (Barcelona, Spain) ([^{68}Ga]DOTA-Tyr3-octreotide, DOTATOC) and ABX GmbH (Radeberg, Germany) ([^{68}Ga]DOTA-Tyr3-octreotate and [^{68}Ga]DOTANal3-octreotide, as DOTATATE and DOTANOC respectively). The synthesis was previously published in Soto-Montenegro et al [1].

Suppl. Table 1: Acquisition parameters for all the scans evaluated in this work.

#Mouse	Tumor model	Days after tumor inoculation	Weight (g)	Tracer	Activity (µCi)	Energy window (keV)
1	PC12	29	29	[^{68}Ga]DOTANOC	30	250-700
2	PC12	29	30	[^{68}Ga]DOTATOC	156	250-700
3	PC12	53	32	[^{68}Ga]DOTATOC	226	250-700
4	AR42J	16	33	[^{68}Ga]DOTATOC	500	100-700
5	AR42J	16	31	[^{68}Ga]DOTATOC	450	100-700
6	AR42J	15	28	[^{68}Ga]DOTATOC	300	100-700
7	Meningioma	16	29	[^{68}Ga]DOTANOC	250	100-700
8	Meningioma	7	28	[^{68}Ga]DOTATOC	480	400-700
		13	31	[^{68}Ga]DOTATOC	550	400-700
		20	36	[^{68}Ga]DOTATOC	650	400-700
9	Meningioma	7	28	[^{68}Ga]DOTATOC	535	400-700
		13	30	[^{68}Ga]DOTATOC	500	400-700
10	Meningioma	7	30	[^{68}Ga]DOTANOC	500	400-700
		14	31	[^{68}Ga]DOTANOC	480	400-700
11	Meningioma	7	30	[^{68}Ga]DOTATATE	600	400-700
12	Meningioma	7	28	[^{68}Ga]DOTATATE	625	400-700
		15	33	[^{68}Ga]DOTATATE	547	400-700
		21	39	[^{68}Ga]DOTATATE	474	400-700

Data acquisition and reconstruction parameters

The tracers were injected into the tail vein (436 ± 172 μCi activity) and scanned for 60 minutes, 30 minutes after injection. CT images (340 mA, 40 KV, 360 projections and 8 frames/projection) were reconstructed using a Feldkamp algorithm, obtaining images with an isotropic voxel size of 0.125 × 0.125 × 0.125 mm^3 [2]. PET images were reconstructed using a fully 3D–OSEM (Ordered Subset Expectation Maximization) algorithm [3], with a voxel size of 0.3875 × 0.3875 × 0.7750 mm^3 and below 1 mm^3 achievable spatial resolution [3]. Decay and dead-time corrections were applied. For the estimation and subtraction of the background counts due to scatter and random coincidences, we followed a method based on Monte Carlo simulations, implemented on PeneloPET [4] according to the following procedure.

- First, we obtained a 3D-OSEM image without any background subtraction. Using the CT information, we set to zero the activity values in all voxels where there is no material, because no activity should be present there.
- Using the image obtained in the previous 3D-OSEM reconstruction as the activity source distribution for the simulation we performed a Monte Carlo simulation with the same settings of each acquisition, and scattered and random counts in a LOR histogram were obtained.
- Finally, we included the estimated scatter and randoms counts as additive terms within a new 3D-OSEM reconstruction procedure, obtaining an image with scatter and randoms corrected.

Positron range correction

The PRC is performed during the reconstruction procedure, following the steps described below (see [5] for further details):

- Analytical calculation of the PR blurring kernel for different tracers and tissues: The PR distributions for the most common radionuclides used in PET were obtained using Monte Carlo simulations with PeneloPET [4]. For the ^{68}Ga-based tracers considered in this work, the radial integrated range distribution (*g3D(r)*) used for the PRC can be modeled with the analytical expression:

$$g_{3D}(r) = C\left[(a \cdot r + 1)\left(1 - \frac{r}{r_0}\right)^n - \frac{\varepsilon}{(r)^n}\right] \quad (1)$$

where a, r_0, n and ε are parameters fitted with a genetic algorithm [6]. C is a constant employed to scale g_{3D} to the data while r_0 represents the maximum PR in the tissue of interest, which is equivalent with the statistical definition of maximum positron range, as given in [7]. For ^{68}Ga-based tracers and water as propagation media, the values of the fitting parameters are: a = 2.41 mm^{-1}, r_0 = 8.98 mm, n = 3.27, ε = 5.2 × 10^{-5}. The profiles for other tissues are obtained scaling by the electronic density of material, using the expression:

$$r_{scaled} = r\frac{\rho_e}{\rho_e^{water}} \quad (2)$$

where R is the unscaled distance traveled by the positron, ρ_e is the electronic density of the material and ρ_e^{water} is the electronic density of water.

- Building PR blurring kernels from the segmented CT image: These kernels are computed only once for each segmented CT image, which provides density information. This PR kernel is then applied during image reconstruction. A four-tissue threshold-based segmentation was made from Hounsfield Units (HU) values measured in the co-registered CT image. The four segmented tissues were: air (HU < -1000), lung (-1000 < HU < -200), water-like tissue (-200 < HU < 800) and bone (HU > 800). The CT image was down-sampled to PET resolution before segmentation. Two models for the blurring kernels were implemented and evaluated in this work:

  Tissue-dependent correction with homogeneous, isotropic kernel (TD-PRC): the blurring kernel is taken from the material where the positron is emitted, irrespectively of the surrounding media. The

blurring is thus homogeneous and isotropic. The PR blurring kernel, also referred to as the annihilation Point Spread Function (aPSF), can be obtained from the g_{3D} analytic distribution defined above:

$$aPSF\left(r_{eq}^{jj'}\right) = \frac{g_{3D}(r_{eq}^{jj'})}{\left(r_{eq}^{jj'}\right)^2} \tag{3}$$

where $r_{eq}^{jj'}$ is given by:

$$r_{eq}^{jj'} = r^{jj'} \cdot \rho_j \tag{4}$$

where $r^{jj'}$ is the geometrical distance between voxels j and *j'* and ρ_j is the density at voxel *j*.

Tissue-dependent and spatially-variant correction (TDSV-PRC): the blurring kernel takes into account not only the material at which the positron is emitted but also the different materials that the positron travels by until it annihilates. First, the tissue-boundaries are automatically detected from the segmented CT image. Then, we determine whether there is any boundary close to each voxel in the image, at a distance smaller than the kernel size. If not, the voxel is tagged so that any emission from it will be blurred with a homogeneous kernel adequate to the tissue present at that voxel. If there are tissue-boundaries close to the voxel considered, the blurring kernel is computed taking into account the different densities of every tissue surrounding the voxel. To this end, for each target voxel j_0 of the blurring kernel we obtain the densities of the voxels associated with the line connecting the originating voxel *j* and the target voxel j_0. The water-equivalent distance between j and j_0 is computed by using a scaling of the mean density of all the voxels associated with the line connecting the originating voxel j and the target voxel j_0. This average density (ρ_m) is calculated as:

$$\rho_m = \frac{1}{N} \sum_{n \in L(j,j')} \rho_e^{(n)} \tag{5}$$

L(j,j') is the line connecting the voxels *j* and *j',* N is the total number of voxels associated with *L(j,j')* and $\rho_e^{(n)}$ is the electronic density of each voxel. The water-equivalent distance $r_{eq}^{jj'}$ between *j* and *j'* is given by:

$$r_{eq}^{jj'} = r^{jj'} \cdot \rho_m \tag{6}$$

Where $r^{jj'}$ is the geometrical distance between j and *j'* and ρ_m is the mean density from (4).

- Incorporation of the PR blurring kernels into the reconstruction algorithm: The PR blurring kernel is employed during the forward projection step in the iterative reconstruction procedure. The PR-corrected OSEM (PR-OSEM) algorithm can be described as follows:

$$x_j' = x_j \frac{\sum_i A_{ij} \left(\frac{y_i}{\sum_j A_{ij} \tilde{x}_j} \right)}{\sum_i A_{ij}} \quad (7)$$

where $\tilde{x}_j$ is the image blurred by PR that is forward projected. $\tilde{x}_j$ is obtained filtering the initial image with a blurring function corresponding to the aPSF range profile (defined in Eq. 2) of the emitter present at voxel j:

$$\tilde{x}_j = x_j \otimes aPSF = \frac{\sum_{j'} x_{j'} \cdot aPSF(r_{eq}^{jj'})}{\sum_{j'} aPSF(r_{eq}^{jj'})} \quad (8)$$

where the filtering is extended to all the *j'* neighboring voxels of *j*, $x_{j'}$ is the activity of the initial image in voxel *j'*, and $aPSF(r_{eq}^{jj'})$ is the value of the aPSF with origin in *j*, at voxel *j'*.

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