

# Optimizing reconstruction parameters for quantitative $^{124}\text{I}$ -PET in the presence of therapeutic doses of $^{131}\text{I}$

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## Original research

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# Abstract

**Purpose** To determine the accuracy of quantitative  $^{124}\text{I}$  PET imaging in the presence of therapeutic levels of  $^{131}\text{I}$ .

**Material and Methods** Multiple PET images were acquired using a NEMA IEC phantom with spheres containing 0.4 MBq/cc of  $^{124}\text{I}$  and increasing amount of  $^{131}\text{I}$  activity in the phantom background (0 to 3.76 GBq). Acquisitions were performed on a GE Discovery 710 PET/CT scanner. At each  $^{131}\text{I}$  activity level two scans were acquired, one with the phantom at the center of the field of view (FOV) and one 11 cm off-center. Images were reconstructed with an ordered subset expectation maximization (OSEM) algorithm using between 1 and 25 iterations of 16 subsets. Results were evaluated visually and by comparing the  $^{124}\text{I}$  activity relative to the baseline PET performed in the absence of  $^{131}\text{I}$ .

**Results** The presence of  $^{131}\text{I}$  within the PET FOV added to the random coincidence rate, to dead-time and to pile-up within the PET detectors. Using our standard clinical reconstruction parameters, the image quality and quantitative accuracy suffered at  $^{131}\text{I}$  background activities above 1.4 GBq. However, increasing the number of iterations resulted in dramatic improvements in image quality and quantitative accuracy. Projection space measurements suggest that the dead time corrections implemented on the scanner perform well even at the highest singles count rate tested (52 Mcps).

**Conclusion** This study shows that  $^{124}\text{I}$  quantitative PET is feasible in the presence of large amounts of  $^{131}\text{I}$  on a GE D710. The high random coincidence fraction slows the reconstruction convergence rate, therefore iterations equivalent to at least 8x16 are recommended.

## Introduction

Targeted radionuclide therapies (TRT) provide a unique opportunity for the concomitant use of theranostic radionuclide pairs to allow more precise patient specific dosimetry measurements and to better assess treatment follow-up. For pre-therapy dosimetry, a diagnostic level of radiotracer is injected to the patient, followed by serial blood sampling and imaging [1, 2]. This information is used to estimate the patient dose distribution for the planned therapy with the assumption that the dose will scale linearly with the radioactivity injected. It is possible, however, that this assumption of linearity is in some cases mistaken. In the context of radionuclide therapy with  $^{131}\text{I}$ -Iodide, we considered comparing pre-therapy PET images made using (the more quantitatively accurate)  $^{124}\text{I}$ -Iodide against similar PET images acquired following co-injection of  $^{124}\text{I}$ -Iodide along with the  $^{131}\text{I}$ -Iodide therapeutic dose. For this comparison to be valid, however, we first needed to determine if the presence of large amounts of  $^{131}\text{I}$  within and around the PET field of view (FOV) impacts  $^{124}\text{I}$  quantitation.

Radioiodine therapy (RAI) with  $^{131}\text{I}$  is widely used to treat thyroid cancer [3].  $^{131}\text{I}$  is also used clinically for other therapies such as recurrent or refractory neuroblastoma [4] with Iodine-131-m-iodobenzylguanidine

( $^{131}\text{I}$ -mIBG), a structural analogue of a neurotransmitter. Successful and safe use of TRT requires knowledge of the radionuclide distribution in the patient: accurate quantification of the radiolabel uptake in the lesion and possibly other organs of interest. Since lesion uptake and biodistribution varies from patient to patient, personalized medicine requires patients to be individually imaged. Knowing the patient-specific uptake of the radionuclide targeting agent allows for the customization of the therapeutic plan so that it is consistent with the dose constraints of the dose limiting tissues [5].

Different approaches for  $^{131}\text{I}$  pre-therapeutic dosimetry have been used. Pacini *et al.* injected a low dose of  $^{131}\text{I}$  for pre-therapeutic SPECT scan imaging [6]. However,  $^{131}\text{I}$  emits high energy gammas that penetrate the septa, degrade image resolution, and presents challenges to quantitative imaging.  $^{123}\text{I}$  has been used as an alternative to  $^{131}\text{I}$ , producing higher quality images afforded by the lower 160 keV photon emission energy, and at lower radiation dose per unit administered activity. However, the 13.2-hour half-life of  $^{123}\text{I}$  limits the ability to perform late time point imaging, important for the estimation of the dosimetry for many radiopharmaceuticals. Alternatively, the positron-emitter  $^{124}\text{I}$  has been proposed for pre-therapy lesion dosimetry[7]. The combination of the 4.2-day half-life of  $^{124}\text{I}$  and the quantitative accuracy of PET imaging makes this iodine isotope well suited for radioiodine dosimetry applications. Beijst *et al.* studied the difference in lesion detectability between  $^{131}\text{I}$ -SPECT and  $^{124}\text{I}$ -PET imaging and found that  $^{124}\text{I}$ -PET offers better image quality for similar activity concentrations [8, 9].

The clinical value of pre-therapeutic dosimetry is still being debated due to the uncertainty surrounding whether the uptake of the pre-therapeutic and therapeutic doses is linear. It is possible that the radioiodine tracer dose given before therapy might change the tissue's avidity for radioiodine or the radiolabeled carrier molecule. This affect could be pharmacologic or potentially radiologic with the latter often referred to as "stunning". Quantitative  $^{124}\text{I}$ -PET before and during therapy could provide new information on the accuracy of pre-therapy dosimetry. A few phantom studies have been published. Lubberink *et al.* looked at optimizing acquisition parameters (energy window) for 2-D and 3-D  $^{124}\text{I}$ -PET imaging with 75 MBq of  $^{131}\text{I}$  in the background of an IEC phantom, with images acquired on an ECAT EXACT HR + scanner (CTI/Siemens) [10]. They observed a loss in image quality compared to  $^{124}\text{I}$ -PET alone, but they do not report on  $^{124}\text{I}$  quantification accuracy and their results cannot be extrapolated to a newer scanner and reconstruction algorithm. In a more recent study, Braad *et al.* [11] measured the accuracy of quantitative  $^{124}\text{I}$ -PET on a GE 690PET/CT scanner. They report a mean recovery coefficient of 0.8 for the 37-mm sphere of the NEMA-IEC phantom filled with mixed 452 kBq ml of  $^{124}\text{I}$  and 22 MBq ml of  $^{131}\text{I}$ .

In this study, we investigate the capability of performing quantitative  $^{124}\text{I}$  PET imaging to determine lesion uptake in the presence of therapeutic activities of  $^{131}\text{I}$ .

## Materials And Methods

### Iodine Isotopes

$^{131}\text{I}$  decays by beta minus emission, with an 8.02d half-life making it well suited for radionuclide therapy applications. In 81% of decays a 364 keV gamma is also emitted and in  $\sim 7\%$  a 637 keV gamma is produced. Although there are no coincident emissions among these gammas, they do fall within the energy window (425–650 keV) used by the PET camera to detect the 511 keV annihilation photons. Given large enough quantities of  $^{131}\text{I}$  within or near the PET field of view (FOV), these will add considerably to detector dead time and pile-up and can produce a significant number of random coincidence events, adding both noise and potential quantitative bias to the PET images. Bremsstrahlung emissions resulting from the  $^{131}\text{I}$  beta particles (predominantly  $E_{\text{max}}$  equal to 606.3 and 333.8 keV) are of low yield and therefore their contribution to the PET imaging signal is expected to be negligible.

$^{124}\text{I}$  decays 77% by electron capture and 23% by positron emission, the latter of which allows its distribution in patients to be precisely assessed using a PET scanner. One half of the positron decays are emitted in a cascade that includes a 602.7 keV gamma (a.k.a. a prompt gamma) produced well within the timing window used to identify annihilation photon coincidence pairs in PET. The energy of this photon is within the PET energy acquisition window and therefore coincidences between it and one of the photons of the annihilation pair cannot be differentiated from a true annihilation photon coincidence. Consequently, these events can produce spurious coincidence events that contribute to an additional background signal which can affect the quantification if left uncorrected [12, 13]. GE PET cameras correct for these cascade coincidences by including an additional constant parameter when performing a fit of the modeled scatter distribution during the scatter correction operation within the image reconstruction algorithm. The use of a constant during this fit assumes that the cascade coincidence distribution is uniform throughout projection space.

## **Phantom**

PET scans were performed using a NEMA IEC body phantom (24.1 x 30.5 x 24.1 cm, 9.7 L) containing a lung insert and six fillable spheres of various diameters: 10, 13, 17, 22, 28, and 37 mm. All spheres were filled with 0.4 MBq/cc of  $^{124}\text{I}$ . A baseline PET scan was acquired with a cold (i.e. no radioactivity) water-filled background. Subsequent PET images were acquired with increasing amounts of  $^{131}\text{I}$  in 740 MBq increments up to 3.7 GBq. For each scan the phantom was carefully placed back in the same position using the laser alignment lines and markers on the PET table. PET scans at each background activity level were acquired with the table at a height that centered the lung insert within the FOV and again with the table raised to its maximum height, resulting in “off-center” images. These same two table heights were used for all background activity levels, resulting in two groups of scans (centered and off-center) with all scans within a group spatially registered to one another.

## **PET/CT acquisition and reconstruction**

All scans were acquired on a Lutetium yttrium orthosilicate (LYSO) GE Discovery 710 PET/CT scanner (GE Medical Solutions, Waukesha, WI, USA) in time-of-flight mode, for 8 minutes using a single bed position centered over the axial extent of the phantom. PET images were reconstructed initially using our standard clinical reconstruction protocol: a 3D-ordered subset expectation maximization (OSEM)

reconstruction algorithm with 2 iterations, 16 subsets and a 128x128x47 matrix (pixel spacing of 5.46875 x 5.46875 mm). Additional image reconstructions using between 1 and 25 iterations were also performed, and for two of the image sets, reconstruction was performed using 500 iterations. The CT scan parameters were 120 kV, 70 mA, 700 mm field of view (FOV), 1.25 mm slice thickness, and 512 x 512 matrix size.

### **Data Analysis in Image Space**

Centered and off-center scans were registered to one another using rigid body transforms (HybridViewer v4.0.0, Hermes Medical Systems). Spherical volumes of interest (VOIs) 5.5 cm in diameter were drawn on the baseline scan centered over each sphere containing  $^{124}\text{I}$ . A seventh VOI sphere was placed over an area containing only background. All VOIs were copied and applied to the other image sets. The large margins of the VOIs around the physical spheres were purposely drawn in an attempt to capture all the radioactivity emanating from each sphere (see Supplemental Figure S1). Because the background  $^{124}\text{I}$  activity was known to be zero, the activity concentration of the sphere itself could be determined by taking the total activity inside the VOI and dividing it by the physical sphere's actual volume. In some cases, the spheres contained a small air bubble seen on the CT. For these spheres, the volume was adjusted using an estimate of the air bubble volume based on the CT image. Concentration measurements were also made using a small VOI (25 mm diameter) placed in the center of the largest containing sphere (37 mm diameter) from images reconstructed with between 1 and 25 iterations, using 16 subsets. For all sphere measurements the  $^{124}\text{I}$  activity concentration was decay-corrected to the time of the first scan's acquisition.

### **Data Analysis in Projection Space**

Region of interest measurements were taken from the line-of-response (LOR) data in projection space. In these measurements only the LORs perpendicular to the scanner axis were included (i.e. the oblique angles were excluded). Each ROI included the 25 LORs (block of 5x5 pixels) passing through the approximate center of the largest sphere. Thus, it was necessary to adjust the position of the ROI so that it traced a sinusoidal path as a function of the radial angle of the LOR rays (see video in Supplemental data S2). The mean of the ROIs over all angles was measured. In addition, an ROI of identical size and placement as a function of angle but offset in the axial dimension was used to sample only background activity (i.e. never sampling activity from any of the hot spheres). Measurements were taken from the raw prompts, random coincidences (estimated from singles), scattered coincidences (modeled), raw true coincidences (prompts minus random and scatter), and fully corrected true coincidence projection data sets (i.e. trues corrected for dead-time, pile-up and attenuation).

## **Results**

### **Activity Quantification when using Clinical Reconstruction Parameters**

The initial measurements of the  $^{124}\text{I}$  activity concentration were based on PET images reconstructed using our standard clinical reconstruction parameters, 2 iterations of the OSEM algorithm utilizing 16

subsets (2x16). Based on these images the apparent activity in the spheres as a function of  $^{131}\text{I}$  background activity differed depending both on sphere size and the position of the phantom within the FOV (Fig. 1a and 1b). For the centered phantom, apparent activity concentration in the larger spheres tended to decrease slightly with increasing background activity, whereas the smaller spheres increased dramatically as the  $^{131}\text{I}$  activity increased. The increase for the small spheres was attributable to the way the concentrations were calculated. We drew oversized VOIs seeking to capture all the activity emanating from each sphere assuming that the true background outside the spheres was zero. The results here, however, suggest that the apparent background was above zero in these images. For the off-center scans, the measured activity in the four largest spheres was stable up to about 2.2 GBq of background  $^{131}\text{I}$ , but dropped precipitously for higher background activities. For the two smallest spheres (13- and 10-mm diameter), the measured activity concentration was quite variable, at times either increasing or decreasing in the presence of additional background  $^{131}\text{I}$ . In general, the small spheres were difficult to visualize at  $^{131}\text{I}$  activities above 2.2 GBq.

### **Relative Activity Quantification taken in Projection Space**

To determine the source of the quantitative errors seen at high  $^{131}\text{I}$  background levels, we decided to take measurements from the raw histogrammed projection data with and without various corrections and also from the random and scatter coincidence corrections themselves. Examples of this data are shown in Figs. 2a-d each of which contains a single projection angle of the raw LOR “true” coincidences (i.e. prompts corrected only for random and scattered coincidences, a – centered and b – off-center) and also with all corrections applied (c – centered and d – off-center). Within each image of the projections, separate scans with different amounts of  $^{131}\text{I}$  background have been stacked on top of one another with corresponding  $^{131}\text{I}$  background activity levels indicated in the text at the left. In these images, green indicates positive counts and red indicates LORs for which the random and scatter count estimates exceeded that of the measured prompts. Although the spheres sometimes overlapped depending on the angle of the projection (and thus the measurements cannot be said to be always of a single sphere), equivalently made measurements still allow for comparisons among the scans with differing background.

As can be appreciated from Figs. 3a and 3c (centered or off-center scans, respectively), the random coincidences measured from the LORs passing through the largest sphere increase approximately with the square of the  $^{131}\text{I}$  background activity, overtaking the uncorrected true coincidences at about 2.2 Gbq and ultimately outnumbering the trues by several fold. Over this same range of background  $^{131}\text{I}$  activities the true and scattered coincident events decrease consistently with the increasing dead-time and despite the constant amount of  $^{124}\text{I}$  present. Counts sampled from the LORs passing through the background region (Figs. 3b and 3d) show random and scattered coincidence levels similar to that in Figs. 3a and b. The true coincidences, however, are appropriately near zero regardless of the background  $^{131}\text{I}$  activity level suggesting that the random and scatter are accurately estimated.

In Fig. 4a (centered phantom) it can be seen that the dead-time correction is also functioning properly, yielding an essentially constant level of true counts from the LORs passing through the large sphere regardless of the background  $^{131}\text{I}$  level (note – the attenuation correction has also been applied here but this correction is not at all impacted by the presence of  $^{131}\text{I}$ ). When the phantom is imaged off-center the corrected trues appear to have just a slight decline with increasing background  $^{131}\text{I}$  (Fig. 4b).

### **Rate of Convergence**

Given that after all corrections were applied in projection space the resulting number of counts emanating from the  $^{124}\text{I}$  present in the spheres was constant across all background levels, we were left to explain why the post image reconstruction results were inaccurate (see again Fig. 1a and 1b). Therefore, we sought to look at the rates of convergence for the largest sphere as impacted by the  $^{131}\text{I}$  background activity level. Based on the plots seen in Figs. 5a and 5b (centered and off-center phantoms, respectively) it is apparent that increasing amounts of  $^{131}\text{I}$  background activity cause a marked reduction in the rate of convergence of the iterative image reconstruction algorithm. For both the centered and off-center phantoms with background  $^{131}\text{I}$  activity levels up to about 1.5 GBq, just two iterations were sufficient to achieve concentrations close to the final value, but with larger amounts of  $^{131}\text{I}$  in the background (and especially for the off-center phantom) stopping at two iterations incurred errors up to 50%.

### **Activity Quantification when using High Number of Iterations**

To circumvent convergence related inaccuracies, we re-reconstructed all images using 25 iterations of 16 subsets. Reconstruction with 25 iterations improved the quantitative accuracy of  $^{124}\text{I}$ -PET images compared to images reconstructed with 2 iterations, for all sphere sizes and  $^{131}\text{I}$  activity concentration levels (Fig. 6a and 6b) except for the image acquired with the phantom in the off-center position with 3.76 GBq of  $^{131}\text{I}$ , which showed a modest decrease in  $^{124}\text{I}$  activity concentration for all spheres. Moreover, the image quality of PET images reconstructed with 25 iterations were comparable to the baseline PET images (Fig. 7a and 7b). The image reconstructed with 2 iterations (left) has spheres that are not clearly defined and appear oval-shaped. The smallest two spheres are not discernable.

In the image on the right, reconstructed with 25 iterations, all six spheres are clearly defined, but while the background level is reduced, some spurious background activity remains (Supplemental Fig. 3). Further iterations applied to the two scans with 3.76 GBq of  $^{131}\text{I}$  in the background resulted in further reductions in background, but the reduction was only an additional 30% at 500 iterations (data not shown). Relatively to the radioactivity concentrations in the spheres, however, these background levels are all extremely small ( $\sim 0.25\%$  at 25 iterations).

## **Discussion**

The results of this study show that quantitative  $^{124}\text{I}$  PET-imaging can be done in the presence of therapeutic amounts of 3.76 GBq  $^{131}\text{I}$  within the GE D710 scanner 16.2 cm FOV if 25 iterations are used during the reconstruction. This corresponds to an activity within a patient of possibly 4 or more times this

amount. Typically, in the clinical setting, image reconstructions are performed with the OSEM algorithm using between 2 and 4 iterations with subsets numbering roughly between 10 and 30. But we found that at the highest levels of  $^{131}\text{I}$  tested, increasing the number of iterations to 25 improves the image quality and  $^{124}\text{I}$  activity quantification accuracy. Figure 5 suggests that 25 iterations are not necessarily needed, and 8 iterations would be enough to approach convergence. We speculate that this is due to the incoherence in LOR counts implicit to the noise added by  $^{131}\text{I}$  in the form of random coincidences. Careful examination of Figs. 2 and 4 indicates that while the overall mean of the LORs passing through the  $^{124}\text{I}$  filled spheres is positive, individual LORs vary greatly sometimes extending down to negative counts. When these LORs are implicitly sampled during the reconstruction process, we believe that this lack of coherence may be slowing convergence. We tested this hypothesis by artificially adding noise to the projection data for the centered phantom with  $^{131}\text{I}$  in the background (data not shown) and this caused a similar delay in convergence.

The  $^{131}\text{I}$  gammas, in addition to the greatly increasing noise and dead time (the mean dead time per pixel increased from 1.02 without background activity to 3.78 for the off-center scan with 3.76 GBq of  $^{131}\text{I}$  in the background), also caused a high degree of pile-up in all detector blocks. This can best be appreciated by looking at the raw prompt counts in projection space (Supplemental Fig. 4a and 4b). Pile-up causes scintillation events occurring within a PET detector block to tend to appear to be positioned at the center of the block. Thus, each of the “dots” discernable in Figure S4 corresponds to a detector block. It is also worth noting that both pile-up and the overall random events, prompts and dead time are not uniform when the phantom is positioned off-center (see comparison between Supplemental Fig. 4a and 4b). The GE D710 image reconstruction includes a correction for pile-up which along with the dead-time and other corrections has worked remarkably well in this data. However, it is conceivable that small inaccuracies in these (large) corrections, might explain the inaccuracies seen particularly in the off-center phantom at the highest  $^{131}\text{I}$  background level. For example, in Fig. 4b we see that the average number of trues over a region of the background is slightly negative, suggesting an overcorrection of either scatter or the number of random events in that region. We hasten to point out though that this was only true of the off-center phantom and it would be very unlikely to encounter a clinical dataset this poorly placed.

## Conclusions

The results of this study show that concomitant  $^{124}\text{I}$ -PET imaging for patients undergoing  $^{131}\text{I}$  therapy is feasible and should provide accurate activity quantification and satisfactory image quality for activities up to 3.76 GBq of  $^{131}\text{I}$  in the background. This result likely extends to other PET models from GE that have the same FOV size and share its method of dead time determination and correction. The corrections applied by the data prior to reconstruction appear to be accurate but noise in the data appears to slow the rate of convergence during image reconstruction. Increasing the number of iterations above what is typically used clinically greatly improves quantitative accuracy and image quality.

## Declarations

### **Ethics Approval and Consent for publication:**

This section is not applicable since there are no patient images or information; nor were any animal experiments performed. This manuscript contains only studies conducted on phantoms. There are also no reproduced images or data from another publication in this submitted manuscript.

### **Availability of data and materials:**

This study involved measurements with phantom only and contains no clinical data. All the image data and analysis results are presented in the manuscript. The original PET/CT images will be made available upon request.

### **Competing Interests and Funding:**

This work was funded by NCI [R01 CA201250](#) (PIs: Steven M. Larson, John L. Humm and Michael Tuttle) entitled "*<sup>124</sup>I-NaI PET: Building block for precision medicine in metastatic thyroid cancer*" and the NCI Cancer Center Support Grant P30 CA008748 (PI Craig Thompson)

### **Authors contributions:**

Dr. Louise Fanchon performed the phantom measurements, assisted in the data analysis and wrote the initial draft of the manuscript.

Dr. Bradley Beattie assisted with the phantom measurements, performed most of the image processing and data analysis, generated several of the manuscript figures and assisted with manuscript editing.

Mr. Keith Pentlow MS assisted with the phantom measurements, data analysis and manuscript editing

Dr. Steven Larson provided valuable input to the design of the experiments and supported the experimental costs through grant funding.

Dr. John Humm provided oversight of all experiments and data analysis and assisted in editing the manuscript.

### **Disclosure of potential conflicts of interest:**

The authors declare that they have no conflict of interest.

### **Ethical approval:**

This article does not contain any studies with human participants or animals performed by any of the authors.

### **Informed consent**

Not applicable

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