Towards tracer dose reduction in PET studies: Simulation of dose reduction by retrospective randomized undersampling of list-mode data

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Abstract

Objective: Optimization of tracer dose regimes in positron emission tomography (PET) imaging is a trade-off between diagnostic image quality and radiation exposure. The challenge lies in defining minimal tracer doses that still result in sufficient diagnostic image quality. In order to find such minimal doses, it would be useful to simulate tracer dose reduction as this would enable to study the effects of tracer dose reduction on image quality in single patients without repeated injections of different amounts of tracer. The aim of our study was to introduce and validate a method for simulation of low-dose PET images enabling direct comparison of different tracer doses in single patients and under constant influencing factors. **Methods:** ^{18}F-fluoride PET data were acquired on a combined PET/magnetic resonance imaging (MRI) scanner. PET data were stored together with the temporal information of the occurrence of single events (list-mode format). A predefined proportion of PET events were then randomly deleted resulting in undersampled PET data. These data sets were subsequently reconstructed resulting in simulated low-dose PET images (retrospective undersampling of list-mode data). This approach was validated in phantom experiments by visual inspection and by comparison of PET quality metrics contrast recovery coefficient (CRC), background-variability (BV) and signal-to-noise ratio (SNR) of measured and simulated PET images for different activity concentrations. In addition, reduced-dose PET images of a clinical ^{18}F-FDG PET dataset were simulated using the proposed approach. **Results:** ^{18}F-PET image quality degraded with decreasing activity concentrations with comparable visual image characteristics in measured and in corresponding simulated PET images. This result was confirmed by quantification of image quality metrics. CRC, SNR and BV showed concordant behavior with decreasing activity concentrations for measured and for corresponding simulated PET images. Simulation of dose-reduced datasets based on clinical ^{18}F-FDG PET data demonstrated the clinical applicability of the proposed data. **Conclusion:** Simulation of PET tracer dose reduction is possible with retrospective undersampling of list-mode data. Resulting simulated low-dose images have equivalent characteristics with PET images actually measured at lower doses and can be used to derive optimal tracer dose regimes.

Introduction

In combination with morphologic imaging in the hybrid approach of PET/CT or PET/MRI, PET is an integral part of the diagnostic work up of numerous oncologic, inflammatory, cardiovascular and neurologic disorders.

With the recent introduction of PET/MRI, radiation exposure of hybrid imaging could be reduced compared to PET/CT. Still, radiation exposure resulting from tracer administration contributes significantly to the patient dose and may lead to negative long term effects .

Attempts have been made to define appropriate dose regimes with minimal radiation exposure. To this end, the behavior of surrogate markers for image quality (e.g. signal to noise ratio, contrast recovery, background variability) was extrapolated from higher doses or measured in phantom experiments . However, these quality markers cannot describe the impact of dose reduction on image-based diagnostic decisions.

One possible but elaborate way to define lower bounds for adequate tracer doses would be the gradual reduction of administered doses in large patient populations. However, these lower bounds would depend on numerous parameters including specific scanner hardware and patient physiology. Furthermore, a direct comparison of PET images acquired with different doses within one single patient is not possible due to ethical consideration and because the biologic state and thus tracer distribution largely

varies over time.

As an alternative, the effects of reduced tracer doses on image properties and on diagnosis might be studied if PET images of lower tracer doses could be simulated. This would allow for direct comparison of PET images resulting from different dose regimes in a single patient under the same conditions.

The purpose of this study was to introduce and validate a method for simulation of low-dose PET images originating from PET data measured at a higher administered dose.

Methods

Simulation of PET images with reduced tracer doses
The approach presented in this study is based on the assumption that tracer dose reduction results in a proportional reduction of detected PET events by the same factor. This assumption is supported by recent data describing the relation of PET acquisition time and administered dose (e.g. reducing acquisition time by 50% is comparable to reducing the tracer dose by 50%) . However, reconstructing PET images from reduced acquisition times cannot always be used to simulate reduced tracer administration in vivo, because such a time/dose relation holds only true for short examination times due to the distribution and metabolism of the tracer. Thus, we aimed to develop a method that is independent of such uptake and metabolism effects.

Positron emission tomography data that are stored together with tempreal information of the occurrence of single PET events (list mode format) can be analyzed regarding the occurrence of single PET events. Thus, it is possible to delete single PET events form the list mode data.

The simulation framework proposed in this study is visualized in Figure 1A. A predefined proportion of PET events was randomly deleted from the list mode dataset using an in-house tool (implemented in MATLAB, version R2014b, MathWorks, Natick, MA) resulting in mimicking reduced activity concentration of the radiation source, or in other words a reduced tracer dose (retrospective undersampling of PET data). The predefined proportion of deleted events was the same as the relative tracer dose reduction to be simulated (e.g. 50% of PET events were deleted for simulation of tracer dose reduction by 50%). Subsequently, PET data were reconstructed using a dedicated software tool provided by the vendor (E7 tools, Siemens, Erlangen, Germany).

Phantom measurements and PET reconstruction
The described simulation tool was validated with phantom measurements using a standardized phantom according to the National Electrical Manufacturers Association (NEMA) (Figure 1B).

The phantom body was filled with a background activity of 5.3kBq/mL ^{18}F-fluoride solution in water. The four smaller spheres (10, 13, 17, 22 mm, hot spheres) were filled with activities of 4 times the background activity in one expe-

riment and with 8 times the background activity in a second experiment. The two larger spheres (28, 37mm) were filled with water only (cold spheres).
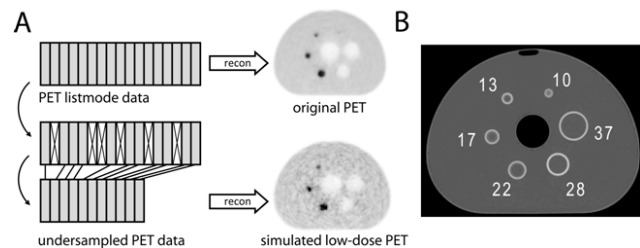
Figure 1. A) Method for simulation of low-dose PET images. PET data are acquired in list mode. Subsequently, a predefined proportion of PET events are randomly deleted resulting in undersampled PET data. Undersampled data are reconstructed resulting in simulated low-dose PET images. B) CT scan of the anthropomorphic phantom used in this study. The phantom body and six spheres of different sizes (10, 13, 17, 22mm: hot spheres and 28, 37mm: cold spheres) are depicted.

Positron emission tomography data were acquired in a combined PET/MR scanner (Biograph mMR, Siemens, Germany). 11 consecutive PET measurements were performed in intervals of 55min (1/2 half life time of ^{18}F) with 20 minutes of acquisition time per measurement. Due to the steady decay of the phantom activity, these measurements were equivalent to reduced tracer doses (tracer dose reduction of 50% after each half-life). Thus, relative to the original dose (100%) tracer reduction down to 3.125% of the original dose was reached after 5 half-lives (100% down to $100\%/2^5=3.125\%$). Data were acquired in list mode. The phantom PET attenuation map was generated using CT attenuation data of the phantom at 120keV.

Positron emission tomography data were reconstructed using the following parameters: 3D ordered-subset expectation maximization (3D-OSEM), 2 iterations, 21 subsets, 4mm Gauss-filter, Matrix size of 344x344.

The first ^{18}F- fluoride PET measurements, corresponding to the full administered tracer doses, were additionally reconstructed using the presented dose simulation tool with simulated dose fractions corresponding to the relative residual tracer activities at the respective 11 measurement time points (100% down to $100\%/2^5=3.125\%$).

Data analysis

Following the NEMA protocol, six circular regions of interest (ROI) were placed within the phantom spheres at the slice of their largest extent with a diameter corresponding to the respective physical sphere diameter. Sixty additional circular ROI were placed within the phantom background for each sphere size.

Fluorine-18-fluoride PET image quality metrics signal-to-noise ratio (SNR) background variability (BV) and contrast recovery coefficients (CRC) were calculated following the NEMA

Table 1. *Comparison of indications on radioiodine remnant ablation for differentiated thyroid carcinoma among different guidelines*

%Dose	100	70.71	50	35.36	25	17.68	12.5	8.84	6.25	4.42	3.125
%Δ BV 4:1	0.0	-8.0	-3.6	-10.5	13.1	-20.2	-18.1	16.7	1.9	12.2	11.4
%Δ BV 8:1	0.0	-1.0	-13.7	-0.7	-11.3	8.9	6.5	-11.1	-5.8	5.0	-1.5
%Δ SNR 4:1	0.0	14.6	8.7	19.2	19.5	-17.4	20,5	-5.1	-0.4	-7.5	-10.0
%Δ SNR 8:1	0.0	1.7	18.6	2.6	15.4	-0.2	-0.6	18.5	5.8	-10.5	20.6
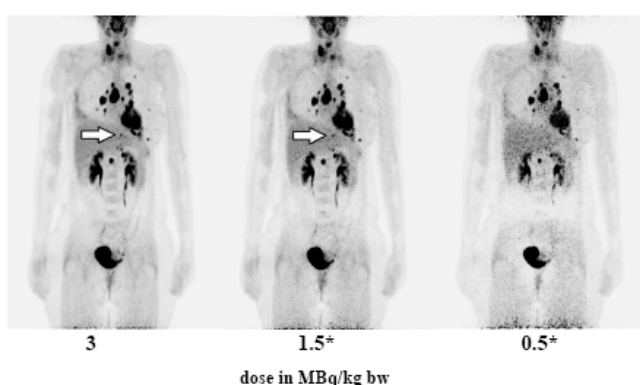
Figure 4. 46 years old patient with metastatic breast cancer. Maximum-intensity-projections of a PET study after injection of 3MBq/kg-bw ^{18}F-FDG (left) and of corresponding simulated reduced-dose PET images (*). Image quality degrades with reduced doses; detectability of small lesions is reduced (e.g. abdominal lymph node, arrow).

measured at lower activity concentrations. Visual image properties as well as the image quality metrics (CRC, BV, SNR) showed concordant behavior in simulated and measured PET images.

It is known that these quality metrics are strongly correlated with lesion detectability in PET images . Attempts have been made in previous studies to define optimal PET tracer doses by estimating the behaviour of these or similar metrics at different doses . However, it is not possible to appreciate the impact of tracer dose reduction on diagnostic accuracy and clinical decisions by simple estimation of image quality metrics. In contrast, the method proposed in our study allows for actual reconstruction and reading of PET images that have equivalent image properties with PET images measured after injection of lower tracer doses. Thus it will be possible to study the effect of tracer dose reduction on diagnostic accuracy and lesion interpretation under a variety of parameters using this approach.

In contrast to simple gating of PET data (i.e. retrospectively reducing examination time), which might similarly allow for dose simulations, randomized subsampling of PET data enables more realistic clinical dose simulations, as dynamic effects of PET measurements (e.g. tracer uptake for longer measurements, patient movement or decay of short-half-life tracers) equally affects measured and simulated data. Especially when examining pediatric patients, bulk motion can occur within the measurement time frame; simple gating of list mode data (e.g. only reconstructing the first part of the measurement) might overestimate image quality by neglecting bulk motion at a later time point. Our suggested method takes these effects into account.

Dose optimization is of importance for patients that have a relevant risk for radiation-induced long-term effects, mainly children and childbearing women. These patients often receive curative oncologic treatment or suffer from non-oncologic disorders requiring repetitive imaging potentially resulting in high cumulative doses . Reduction of PET-induced radiation exposure may not only reduce possible radiation-related risks but may also improve acceptance of PET among patients and referring physicians.

This study has limitations. The assumption that tracer dose reduction is equivalent to a reduction of PET events by the same factor is a simplification of the complex process of PET data acquisition and is probably violated for very high or low doses (due to dead time effects and limited detector sensitivity). However, recent data as well as the experimental results of our study suggest that this central assumption is valid for a wide range of activity concentrations used in clinical PET imaging.

Phantom studies can only simulate the behaviour of image properties in patient studies. We tried to approach a realistic scenario by using dose concentrations and a phantom design mimicking a regular patient study. Still, properties of PET images that are obtained using the proposed simulation approach may vary from actually measured images in patients. However, it is not possible to perform similar validation measurements in patients. Thus, the results of our phantom measurements provide a basis for the application of the proposed approach in clinical studies.

In conclusion, simulation of PET tracer dose reduction is possible with retrospective undersampling of list mode data. Resulting simulated low-dose images have equivalent characteristics with PET images measured at lower doses doses and can be used to derive optimal tracer dose regimes.

Supplement. Dependence of background variability (BV, upper row) and signal-to-noise-ratio (SNR, bottom row) on relative activity concentrations (measured, sold lines and simulated, dashed lines), different sphere-to-background ratios (4:1, left and 8:1, right) and different sphere diameters (color-coded)
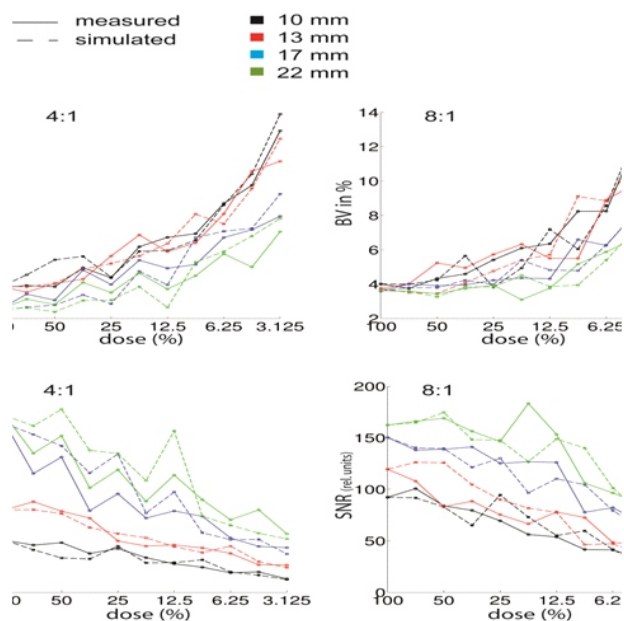
The authors declare that they have no conflicts of interest

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