Published in final edited form as:

Phys Med Biol. ; 63(18): 185002. doi:10.1088/1361-6560/aada26.

Developing an efficient phase-matched attenuation correction method for quiescent period PET in abdominal PET/MRI

Jaewon Yang¹, Jing Liu¹, Florian Wiesinger², Anne Menini², Xucheng Zhu^{1,3}, Thomas A. Hope¹, Youngho Seo^{1,3,4}, and Peder E. Z. Larson^{1,3}

¹Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA

²GE Healthcare, MR ASL Europe, Munich, Germany

³UCSF-UC Berkeley Joint PhD Program in Bioengineering, University of California, San Francisco and Berkeley, CA

⁴Department of Radiation Oncology, University of California, San Francisco, CA

Abstract

Respiratory motion causes misalignments between positron emission tomography (PET) and magnetic resonance (MR)-derived attenuation maps (μ -maps) in addition to artifacts on both PET and MR images in simultaneous PET/MRI for organs such as liver that can experience motion of several centimeters. To address this problem, we developed an efficient MR-based attenuation correction (MRAC) method to generate phase-matched μ -maps for quiescent period PET (PET_Q) in abdominal PET/MRI. MRAC data was acquired with CIRCULAR Cartesian UnderSampling (CIRCUS) sampling during 100 s in free-breathing as an accelerated data acquisition strategy for phase-matched MRAC (MRAC_{PM-CIRCUS}). For comparison, MRAC data with raster (Default) k-space sampling was also acquired during 100 s in free-breathing (MRAC_{PM-Default}), and used to evaluate MRAC_{PM-CIRCUS} as well as un-matched MRAC (MRAC_{UM}) that was un-gated. We purposefully oversampled the MRAC_{PM} data to ensure we had enough information to capture all respiratory phases to make this comparison as robust as possible. The proposed MRAC_{PM-CIRCUS} was evaluated in 17 patients with ⁶⁸Ga-DOTA-TOC PET/MRI exams, suspected of having neuroendocrine tumors or liver metastases. Effects of CIRCUS sampling for accelerating a data acquisition were evaluated by simulating the data acquisition time retrospectively in increments of 5 s. Effects of MRAC_{PM-CIRCUS} on PET_Q were evaluated using uptake differences in the liver lesions (n = 35), compared to PET_Q with MRAC_{PM-Default} and MRAC_{UM}. A Wilcoxon signed-rank test was performed to compare lesion uptakes between the MRAC methods.

MRAC_{PM-CIRCUS} showed higher image quality compared to MRAC_{PM-Default} for the same acquisition times, demonstrating that a data acquisition time of 30 s was reasonable to achieve phase-matched μ -maps. Lesion uptake differences between MRAC_{PM-CIRCUS} (30 s) versus MRAC_{PM-Default} (reference, 100 s) were $0.1\% \pm 1.4\%$ (range of -2.7% to 3.2%) and not significant ($P > .05$); while, the differences between MRAC_{UM} versus MRAC_{PM-Default} were $0.6\% \pm 11.4\%$ with a large variation (range of -37% to 20%) and significant ($P < .05$). In conclusion, we demonstrated that a data acquisition of 30 s achieved phase-matched μ -maps when using

specialized CIRCUS data sampling and phase-matched μ -maps improved PET_Q quantification significantly.

Keywords

PET/MRI; attenuation correction; respiratory motion; compressed sensing

1. Introduction

In positron emission tomography/magnetic resonance imaging (PET/MRI), respiratory motion may result in misalignments between PET and MR-derived attenuation maps (μ -maps) in addition to motion artifacts on both PET and MR images. The misaligned μ -maps introduce qualitative and quantitative errors such as tumor misquantification, misdisplacement, and volume overestimation (Geramifar *et al.*, 2013). For example, a substantial signal loss is often observed around the hemidiaphragm (banana artifact) due to the misaligned μ -maps in PET images, which is well known from PET/computed tomography (CT) studies (Kinahan *et al.*, 2003; Sureshbabu and Mawlawi, 2005). The effect of misaligned μ -maps was also demonstrated in a simulated dynamic MR study (Polycarpou *et al.*, 2014), which justified the importance of phase-matched MR-based attenuation correction (MRAC_{PM}) for thoracic and abdominal PET/MRI.

MRAC_{PM} approaches have been developed to address this problem and consist of two separate MR data acquisitions (Kolbitsch *et al.*, 2018; Grimm *et al.*, 2013; Buerger *et al.*, 2012): First, motion-free μ -maps were acquired at a predetermined respiratory phase (e.g., breath-hold end-expiration or end-inspiration); and second, the μ -maps were deformed to a target phase by motion models derived from separately acquired motion-resolved MR images. In a simulated PET study, an Ultrashort Echo Time (UTE) data was acquired to derive μ -maps and multiple 3D MR volumes were dynamically acquired to derive motion models (Buerger *et al.*, 2012), but this approach required long data acquisitions (11–16 m for UTE and additional time for multiple 3D MR volumetric imaging) and computationally expensive registration and respiratory modeling (3–4 m). In another study of three patients, a high-resolution MR-based motion model was derived from a 3D radial stack-of-stars gradient echo (GRE) sequence that required long data acquisitions (10–12 m) (Grimm *et al.*, 2013). To accelerate MR data acquisition for deriving motion models, instead of 3D volumetric imaging, multiple 2D imaging was employed using a spoiled GRE sequence (3 minutes) (Wurslin *et al.*, 2013) or a fast GRE sequence (1 minute) (Manber *et al.*, 2016). Besides, motion models derived from respiratory-resolved 4-Dimensional (4D) PET without attenuation correction (Fayad *et al.*, 2017) or joint activity reconstruction/motion estimation (Bousse *et al.*, 2016) were also demonstrated without depending on MR data. In a recent clinical PET/MRI study, a development of respiratory-resolved μ -maps was demonstrated using a T1-weighted diagnostic scan without requiring an additional breath-hold MRAC scan, with the data acquisition time of 4 m 30 s (Kolbitsch *et al.*, 2018).

In this paper, we propose a new approach for MRAC_{PM} using pseudo-random CIRCular Cartesian UnderSampling (CIRCUS) k-space sampling as an accelerated data acquisition

strategy during free-breathing (without using a breath-hold), combined with retrospective data sorting and a compressed sensing reconstruction for efficient and robust generation of phase-matched μ -maps. The efficiency of CIRCUS sampling for accelerating a data acquisition was evaluated in comparison with raster (Default) sampling. Also, effects of MRAC_{PM} on PET were evaluated in quiescent period PET (PET_Q) that is a practical and clinical implementation to reduce respiratory motion artifacts by sorting PET signals retrospectively into end-expiration (quiescent period).

2. Methods

2.1. Patient information

The patient study was approved by the Institutional Review Board and all patients signed an informed consent before the examinations. 17 patients suspected of having neuroendocrine tumors or liver metastases based on the clinical indication or referral information had liver-focused ⁶⁸Ga-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-(Tyr³)-octreotide (⁶⁸Ga-DOTA-TOC) PET/MR exams consecutively (Sep 2016 – Apr 2017). The average patient age ($\pm$ standard deviation) was 59.8 years $\pm$ 13.2 (range, 34–77 years) – 61.9 years $\pm$ 7.7 for men and 56.9 years $\pm$ 18.9 for women; The average weight was 78.3 kg $\pm$ 23.1 (range, 43.1–136.1 kg).

2.2. Quiescent period PET (PET_Q)

Time-of-flight (TOF) PET acquisition was performed simultaneously with MR data acquisition (Figure 1) on a SIGNA PETMR (GE Healthcare). The average administered dose was 170.5 MBq $\pm$ 47.9 (range, 103.2–272.3 MBq). The scan duration was 20 minutes and the average time difference between injection and scan was 75.5 minutes $\pm$ 13.5 (range, 52.6–101.7 minutes).

PET_Q is the current clinical protocol in a SIGNA PETMR, implemented by the vendor (GE Healthcare). This approach was demonstrated as a practical and efficient method to reduce respiratory motion artifacts in the literature (Liu *et al.*, 2010; Nyflot *et al.*, 2015). To our knowledge, PET_Q is clinically practical as 50% of PET data from the end-expiration quiescent period forms a single PET frame with reduced motion artifacts but still acceptable signal-to-noise properties. This is why PET_Q is the default for PET motion correction in clinical practice in our department; and accordingly, it is important to develop an efficient and robust MRAC method for improving the quantification accuracy of PET_Q. In the protocol, PET list-mode data were retrospectively sorted into the 30–80% phase bin (0%: end-inspiration) of respiratory cycles for the quiescent period (i.e., end-expiration). The 30–80% phase information was derived from respiratory triggers generated at the 30% phase of each respiratory cycle in the pressure belt system (bellows, GE Healthcare). Then, PET_Q was reconstructed using a TOF ordered subsets expectation maximization algorithm (2 iterations; 28 subsets; matrix size, 256 $\times$ 256 $\times$ 89; voxel size, 1.95 $\times$ 1.95 $\times$ 2.78 mm³; 5.0 mm in-plane gaussian filtering followed by axial 3-slice 1:4:1 filtering) in the offline PET/MR toolbox (REL_1_26, GE Healthcare). Quantitative corrections including normalization, dead time, point-spread function, randoms, scatter, decay, and attenuation were applied during the reconstruction.

2.3. Phase-Matched MRAC using CIRCUS k-space sampling (MRAC_{PM-CIRCUS})

Two-echo Dixon 3D spoiled-gradient echo imaging (acquisition time of 18 s; TR/TE1/TE2, 4.0/1.3/2.6 ms; FA, 5°) is a clinical implementation for generating MRAC images (field of view, 50 cm; matrix size, 256 × 128 × 60; voxel size, 1.95 × 3.9 × 5.2 mm³; interpolated to 1.95×1.95×2.6 mm³) using raster ‘Default’ k-space sampling (Wollenweber *et al.*, 2013). Instead of using the default sampling, we propose to acquire MRAC data using CIRCular Cartesian UnderSampling (CIRCUS) k-space sampling during free-breathing as a possible accelerated data acquisition strategy for phase-matched MRAC (MRAC_{PM-CIRCUS}), as described in Figure 2. The 100 s of data were acquired for determining how much the CIRCUS sampling was able to accelerate the data acquisition, compared to the default sampling. The CIRCUS strategy samples the phase and slice encoding dimensions in a pseudo-random order based on golden angle rotations, acquiring samples repeatedly at the k-space center, which allows accelerated data acquisition combined with compressed sensing reconstruction (Liu and Saloner, 2014); while, the default sampling strategy samples the phase and slice encode dimensions in a sequential, raster order. Briefly, the CIRCUS strategy used a spiral phase encoding pattern with $c = 1.5$, as defined by Eq. 3 in (Liu and Saloner, 2014), and a partial Fourier sampling factor of 0.75 in both phase encoding dimensions. See (Liu and Saloner, 2014) for further details. All other scan parameters were consistent in both the Dixon method and MRAC_{PM-CIRCUS} (TR/TE1/TE2, 4.0/1.3/2.6 ms; FA, 5°; field of view, 50 cm; matrix size, 256 × 128 × 60; voxel size, 1.95 × 3.9 × 5.2 mm³).

MRAC_{PM-CIRCUS} data (i.e., k-space samples) were retrospectively sorted into the quiescent period (same as the clinical implementation for PET_Q) as described in Figure 2: Figure 2a shows the respiratory trace (top) recorded with triggers generated at the 30% phase of each respiratory cycle, describing the phase-based gating method for MRAC_{PM-CIRCUS} data sorting; Figure 2b shows the retrospective simulation of the data acquisition time in increments of 5 s and corresponding CIRCUS samples in k-space at the time points of every 10 s; and Figure 2c illustrates the impact of reduced acquisition time on the image quality of MR in-phase at 10 s, 40 s, 70 s and 100 s. MR in-phase and out-of-phase images were reconstructed by compressed sensing-based motion-compensated reconstruction in the Berkeley Advanced Reconstruction Toolbox (BART, version 0.3.01) based on the following optimization problem:

$$\operatorname{argmin}_{x_t} \frac{1}{2} \|P_t S F x_t - d_t\|_2^2 + \lambda_{TV} \|x_t\|_{TV} + \lambda_s \|\Psi x_t\|_1 \quad (1)$$

where x_t is images (in-phase and out-of-phase) at a motion state t ($t = 1$: 30–80% phase, $t = 2$: other phases), P_t is a mask to choose a different motion state, S is sensitivity maps for using multi-channel receive coils (in our case, as we only use the body coil, sensitivity map is all 1 matrix), F represents the 3D Fourier Transform, TV represents a total variation along each motion state ($\lambda_{TV} = 0.01$), and Ψ is a spatial sparse transformation operator such as a wavelet or total variation ($\lambda_s = 0.01$). Here we empirically chose a spatial total variation operator for Ψ , as it produced reduced undersampling artifacts compared to a wavelet transform. More details are found in the reference (Tamir *et al.*, 2016; Uecker *et al.*).

Water and fat images were generated from the in-phase and out-of-phase images in an Orchestra MR reconstruction toolbox (Orchestra-sdk-1.3–24, GE Healthcare), and water/fat images are automatically converted to pseudo CT followed by μ -map transformation based on segmentation with air, lung and a continuous fat/water method, identically to the clinical implementation developed by the vendor (Wollenweber *et al.*, 2013). All the processes were performed in MATLAB (MathWorks).

2.4. Phase-Matched MRAC using default k-space sampling (MRAC_{PM-Default})

MRAC data acquisition using the default sampling was extended to fulfill 100 s, repeating the default Dixon sequence (18 s) (Figure 1), in order to achieve phase-matched MRAC retrospectively (MRAC_{PM-Default}) (Figure 3). We purposefully oversampled the data during 100 s to ensure that the data provide enough information to capture all respiratory phases to make this comparison as robust as possible. MRAC_{PM-Default} sorted k-space samples into the quiescent period by retrospective soft-gating as depicted in Figure 3: Figure 3a shows the respiratory trace (top) recorded during the data acquisition of MRAC_{PM-Default} and its phase information (middle) derived from respiratory triggers; The weights (bottom) are determined for soft-gating as follows:

$$\begin{aligned} w &= 1 \text{ for } 0.3\text{--}0.8 \text{ (30--80\% phase)} \\ w &= \exp(-4 * \min(p-0.3, p-0.8)) / 0.1 \text{ for other phases} \end{aligned} \quad (2)$$

where w is a weight at each time point for MR signals and p is the fraction of the respiratory phase cycle (0: 0%, 1:100%). For the formula, parameters were empirically determined to give a small weight with a high gradient for MR signals close to the gating boundary but not included in the gating window (30–80% phase). This soft-gating method can provide fully sampled data in k-space faster than the conventional gating (i.e., including only samples at a target phase) by giving small weights to the samples out of the gating window (Jiang *et al.*, 2017). Figure 3b shows the retrospective simulation of the data acquisition time in increments of 5 s and corresponding k-space samples at the time points of every 10 s. Figure 3c illustrates the impact of reduced acquisition time on the image quality of MR in-phase at 10 s, 40 s, 70 s and 100 s and a difference between Un-Matched (UM) and Phase-Matched (PM) MR in-phase images. As k-space samples are removed during retrospective gating according to corresponding respiratory phases, the optimal scan duration for MRAC_{PM-Default} varies according to breathing patterns but 100 s was empirically justified to fill up the k-space sufficiently. Figure 3d depicts Un-Matched MRAC (MRAC_{UM}) data acquisition and corresponding k-space samples, using the 18 s data acquired from the default Dixon sequence without gating to evaluate the clinical merit of MRAC_{PM} for PET_Q. MRAC_{UM} was the worst scenario to show the largest phase mismatch with the phase of PET_Q.

MR in-phase and out-of-phase images were reconstructed using a fast Fourier transform in an Orchestra MR reconstruction toolbox (Orchestra-sdk-1.3–24, GE Healthcare). MRAC-derived μ -maps were automatically generated as described in the section 2.3.

2.5. Evaluation

Pseudo CT derived from MRAC_{PM-CIRCUS} (100 s), MRAC_{PM-Default} (100 s), and MRAC_{UM} (18 s) were visually compared to confirm the followings: MRAC_{PM-Default} can achieve accurate respiratory phase and reduce motion artifacts consistently through retrospective gating (UM versus PM); and MRAC_{PM-CIRCUS} can achieve similar quality of pseudo CT consistently, compared to MRAC_{PM-Default} (CIRCUS versus Default). Here, full 100 s data were used for generating phase-matched pseudo CT to avoid any artifact caused by lack of k-space samples. This quality assurance of phase-matched pseudo CT allowed for the following evaluation of MRAC_{PM-CIRCUS} to validate its capability for accelerating the data acquisition and improving PET_Q quantification.

The capability of the CIRCUS sampling strategy for accelerating MRAC_{PM} was evaluated by simulating the data acquisition time retrospectively in increments of 5 s for MRAC_{PM-CIRCUS} and MRAC_{PM-Default} (Figures 2 and 3). Pseudo CT and μ -maps derived from each subset (5 – 95 s) were compared to those with the full 100 s data, assuming that the full data achieved the highest image quality. Image similarities between each subset (5 – 95 s) and the full data (100 s) were quantified by voxel-by-voxel Pearson's correlation coefficient (CC, %) for non-air voxels. Through this evaluation, an optimal scan time for MRAC_{PM-CIRCUS} was chosen to achieve shorter data acquisition time and higher overall similarity to the images with the full data. As reference, MRAC_{PM-Default} with the full 100 s data was employed as silver standard, without ground truth CT images, for evaluating MRAC_{PM-CIRCUS} with the optimal data acquisition.

Effects of MRAC_{PM-CIRCUS} on PET_Q were evaluated quantitatively and qualitatively for the optimal data acquisition time that was demonstrated in the above. PET_Q were reconstructed using μ -maps derived from MRAC_{PM-CIRCUS} (optimal scan time), MRAC_{PM-Default} (100 s) and MRAC_{UM} (18 s), and their quantitative comparisons were performed for investigating the global effects of data sorting and sampling in the field-of-view through voxel-based comparison and for investigating the local effects of data sorting and sampling in the liver through lesion-based comparison. Lesions were not observed in the 2 out of 17 patients and too large lesions were excluded from the analysis. The number of lesions selected per patient was limited to 3 to avoid a patient-dependent bias for statistical testing and the total number of lesions for the analysis is 35 ($n = 35$, Supplementary Table 1). Maximum standardized uptake values (SUV_{max}) were measured using an open toolkit RT_Image (Graves *et al.*, 2007) and their absolute and relative (%) differences (diff) were calculated. A Wilcoxon signed-rank test was performed to compare SUV_{max} between the MRAC methods. All statistical analyses were performed in MATLAB (MathWorks).

3. Results

The quality of MRAC_{PM} is illustrated in Figure 4. The comparison of pseudo CT derived from MRAC_{UM} and MRAC_{PM-Default} (UM versus PM) shows that. MRAC_{PM-Default} achieved accurate respiratory phase and reduce motion artifacts consistently through retrospective gating; additionally, the comparison of pseudo CT derived from MRAC_{PM-Default} and MRAC_{PM-CIRCUS} (CIRCUS versus Default) shows that MRAC_{PM-CIRCUS} generates pseudo CT almost identical to pseudo CT derived from

MRAC_{PM-Default}. Accordingly, Figure 4 justified that the capability of MRAC_{PM} is consistent without regard to sampling strategies for the full 100 s data acquisition.

Based on the result of Figure 4, Figure 5 demonstrates how quickly the CIRCUS sampling can achieve a reasonable image quality of pseudo CT and μ -map for MRAC_{PM}, compared to the default sampling. Regarding the convergence speed of pseudo CT, MRAC_{PM-Default} took longer than 60 s until converging to $> 80\%$ CC on average (Figure 5a); while, MRAC_{PM-CIRCUS} took only 30 s, representing a 50% reduction in scan time (Figure 5b). The acceleration power of MRAC_{PM-CIRCUS} is illustrated in Figure 6 that compares data acquisition time and corresponding image quality for both MRAC_{PM-CIRCUS} and MRAC_{PM-Default}. Severe errors are observed in segmentation with air/lung and summation of continuous fat/water values for MRAC_{PM-Default} with the data acquisition times of 60 s due to insufficient k-space samples, but no major errors are observed for MRAC_{PM-CIRCUS} even with the data acquisition of 20 s. Regarding the convergence speed of μ -map, MRAC_{PM-Default} took longer than 60 s until converging to 99% CC on average (Figure 5c); while, MRAC_{PM-CIRCUS} took only 15 s, representing a 75% reduction in scan time (Figure 5d). Image resizing with 600 mm reconstruction FOV and Gaussian post filtering with 10 mm full width at half maximum were performed as the default at the final step of converting pseudo CT to μ -map. By this post-processing, the edges of soft tissue (e.g., liver dome) were significantly blurred and a minor segmentation difference at the interface of air, lung, and soft tissue was mitigated in low-resolution μ -maps; as a result, the convergence speed and accuracy was substantially improved in μ -maps (99% in 15 s), compared to pseudo CT (80% in 30 s), for MRAC_{PM-CIRCUS}. Considering the trade-off between data acquisition time and overall image quality of pseudo CT and μ -maps, the MRAC_{PM-CIRCUS} data acquisition of 30 s was chosen as a reasonable compromise to achieve shorter data acquisition time and higher overall similarity to the images with the full data. Therefore, the data acquisition of 30 s for MRAC_{PM-CIRCUS} and the full 100 s data acquisition for the reference MRAC_{PM-Default} were used in the following evaluations.

The scatterplot of voxel-wise PET_Q comparison between MRAC_{PM-CIRCUS} (30 s) versus MRAC_{PM-Default} (reference, 100 s) shows the similarity of both MRAC_{PM} methods using the two different k-space sampling strategies (CIRCUS versus Default) (Figure 7a); while, the scatterplot of voxel-wise comparison between MRAC_{UM} versus MRAC_{PM-Default} shows the global effects of misaligned μ -maps that resulted in substantial underestimation on the voxels affected by the misalignment (Figure 7b).

The lesion uptake differences between MRAC_{PM-CIRCUS} (30 s) versus MRAC_{PM-Default} (reference, 100 s) were small (within a range of $\pm 5\%$) and statistically not significant ($P > .05$), which was summarized in Table 1. The corresponding boxplot of lesion uptake differences shows the local effects of misaligned μ -maps in the liver and confirmed the similarity of both MRAC_{PM} methods using the two different k-space sampling strategies (CIRCUS versus Default) (Figure 8a). However, the lesion uptake differences between MRAC_{UM} versus MRAC_{PM-Default} were slight but largely varying, ranged from -37% to 20% (Figure 8b), which was statistically significant ($P > .05$), as summarized in Table 1. Additionally, several outliers are observed in the lesion uptake differences for MRAC_{UM} (Figure 8b); while, there are no outliers for MRAC_{PM-CIRCUS} (30 s) (Figure 8a),

demonstrating that MRAC_{PM-CIRCUS} can successfully remove localized quantification errors caused by substantially misaligned μ -maps.

Figure 9 illustrates the overall result of the liver-focused analysis demonstrated in the above. In the comparison of MRAC_{UM} to MRAC_{PM-Default} (reference), the overall slight overestimation in the lesion-based analysis (i.e., boxes in Fig 8b) was illustrated as a slight overestimation in liver tissue uptakes (Figure 9; 2nd row, 2nd column), which was correlated with substantially overestimated attenuation coefficients at the mismatched abdominal wall (Figure 9; 4th row, 2nd column). Also, substantially underestimated lesions in the lesion-based analysis (i.e., outliers in Fig 8b) for MRAC_{UM} were observed near the liver dome (Figure 9; 2nd row, 2nd column), which was strongly correlated with substantially underestimated attenuation coefficients near the mismatched liver dome (Figure 9; 4th row, 2nd column). However, in the comparison of MRAC_{PM-CIRCUS} to MRAC_{PM-Default}, despite the μ -map difference (Figure 9; 4th row, 3rd column), the liver dome and skin interfaces, no substantial differences were found in the PET difference images (Figure 9; 2nd row, 3rd column),

4. Discussion

We developed an efficient MRAC method to generate phase-matched μ -maps for respiratory-gated PET_Q in abdominal PET/MRI. MRAC data was acquired during 100 s in free-breathing using CIRCUS sampling as an accelerated data acquisition strategy (MRAC_{PM-CIRCUS}, Figure 2). For comparison, MRAC data with default k-space sampling was also acquired during 100 s in free-breathing (MRAC_{PM-Default}, Figure 3) and retrospectively gated, and used to evaluate MRAC_{PM-CIRCUS} as well as un-matched MRAC (MRAC_{UM}) that is ungated (Figure 4). We purposefully oversampled the MRAC_{PM} data to ensure we had enough information to capture all respiratory phases to make this comparison as robust as possible.

Our results demonstrated that the newly proposed MRAC_{PM-CIRCUS} method achieved phase-matched μ -maps consistently with only 30 s of data acquisition (Figures 5 and 6), achieving the quiescent period and reducing motion artifacts consistently (Figure 4). CIRCUS provides pseudo-random, variable-density undersampling trajectories, which allows flexible interleaving on a 3D Cartesian grid by using a golden-ratio profile for continuous k-space coverage (Liu and Saloner, 2014). Oversampling of the center of k-space plays a key role to accelerate data acquisition for MRAC_{PM-CIRCUS} (Figure 2); while, the substantial variability and slow convergence of MRAC_{PM-Default} (> 60 s) can be explained by missing large portions of k-space data that is removed during retrospective gating (Figure 3). By virtue of the shorter scan time, CIRCUS has less opportunity for any artifact caused by irregular breathing patterns so we would expect on average less residual motion artifacts. The CIRCUS sampling demonstrates a factor of 2 improvement in scan time, and saving of 30 s is particularly significant in whole-body PET/MRI where each bed position is acquired is quite constrained to only 3–4 minutes typically. MRAC_{PM} maybe required in multiple bed positions as well, resulting in greater time saving. A major goal in designing MRAC_{PM} acquisitions is speed, as this frees up the scan time for performing diagnostic MRI. In addition to this 2x savings, the CIRCUS trajectory is suited to respiratory phase resolved

reconstructions as shown in Figure 10. This type of MRI sampling pattern with temporal incoherency is the basis for the recent revolution in motion-resolved MRI (for example, the GRASP/XD-GRASP methods); while, raster sampling patterns are very poorly suited for respiratory phase resolved reconstructions. To our knowledge, there was no study to apply a pseudo-random sampling such as CIRCUS, combined with compressed sensing reconstruction, to accelerate a MRAC data acquisition for generating phase-matched μ -maps.

The evaluation of phase-matched μ -maps on PET_Q was also performed using liver-focused *clinical* data acquired in simultaneous PET/MRI. Our results demonstrated that MRAC_{PM-CIRCUS} maintained accurate PET_Q quantification in comparison to MRAC_{UM} (Figures 7–9, Table 1) by removing a possibility of misaligned μ -maps that cause a slight overestimation in liver tissues and a substantial underestimation for lesions located at the liver dome. These results were analogous to the previous results of a 4D PET/4D CT *phantom* study (Nyflot *et al.*, 2015). The phantom study demonstrated comparative advantages in qualitative and quantitative PET with the use of end-expiration CT-based attenuation correction (CTAC) that was conceptually consistent with our MRAC_{PM-CIRCUS} at the quiescent period (approximately close to end-expiration). Since breathing patterns are generally regular at end-expiration and irregular at end-inspiration (Yang *et al.*, 2016) as illustrated in Figures 2a and 3a, it is beneficial and practical to develop a phase-matched MRAC method only at the quiescent period (or end-expiration), which avoids an issue caused by breathing irregularity that are difficult to manage (Yang *et al.*, 2016).

Based on the previous phase-matched MRAC studies, for the practical use of MRAC_{PM} in clinical applications, it is important 1) to accelerate a data acquisition to save time for other diagnostic MR scans, 2) to combine two-separate MR data acquisitions into the one in order to remove the need of deformable image registration, and 3) to keep 3D MR volumetric imaging instead of multiple 2D imaging. Our approach achieved all the above. In general, the previous methods required data acquisitions twice for motion-free μ -map generation and respiratory motion estimation: Motion-free μ -maps were acquired at a predetermined respiratory phase with a breath-hold end-expiration or end-inspiration instruction, and then the μ -maps were warped into a target respiratory phase using motion models derived from additional high-resolution 3D (Buerger *et al.*, 2012; Grimm *et al.*, 2013) or fast 2D MR imaging (Wurslin *et al.*, 2013; Manber *et al.*, 2016). Besides the longer data acquisitions of separated sequences, compliance issues during breath-hold instructions arise frequently in elder patients, pediatric patients, or patients with hearing impairment; and the use of deformable image registration or complex optimization needs additional quality assurance and processing time.

In a recent clinical PET/MRI study, a development of respiratory-resolved μ -maps was proposed using a T1-weighted diagnostic scan without requiring an additional breath-hold MRAC scan (Kolbitsch *et al.*, 2018), although the scan duration (4 m 30 s) was still long. Our MRAC_{PM-CIRCUS} can also support reconstruction of respiratory-resolved (or 4D) MRAC images at multiple respiratory phases (Figure 10). As 30 s of data acquisition time is optimized for MRAC_{PM-CIRCUS} at the quiescent period, at least 60 s or longer acquisition would be required for an acceptable quality of 4D MRAC_{CIRCUS} whose optimal scan

duration is dependent on breathing patterns and the number of bins. In theory, 4D MRAC is expected to provide optimal attenuation corrections for 4D PET; however, respiratory motion artifacts or irregular breathing patterns in implementation of 4D MRAC and 4D PET sorting can degrade the benefit of 4D MRAC, as demonstrated in the phantom study of 4D CTAC (Nyflot *et al.*, 2015). Although respiratory-resolved μ -maps are prepared, a misalignment between MRAC and PET data is likely to occur if a 4D MRAC scan (e.g., 2 minutes) is considerably shorter than a PET scan (e.g., 10 minutes) as usual and breathing patterns change substantially after the 4D MRAC data acquisition, specifically at end-inspiration. As mentioned in the above, breathing patterns are generally irregular at end inspiration (Yang *et al.*, 2016), so that it is challenging to maintain phase-matched PET/MRAC consistently at the end-inspiration phase. Since it is difficult to compensate for irregular breathing patterns after data acquisition, it may be more efficient and practical to guide patients to regularize their breathing patterns with the help of a breathing guidance system such as an audiovisual biofeedback (Yang *et al.*, 2016).

Despite irregular breathing at end inspiration, it is feasible to perform motion-compensated image reconstruction (MCIR) (Manber *et al.*, 2016) or event-by-event respiratory motion correction (Ren *et al.*, 2017) using full PET data and MR-based motion models. Manber *et al.* demonstrated the performance of MCIR using a motion model derived from 2D multi-slice GRE, assuming the non-rigid registrations (NRR) worked perfectly; however, occasional registration errors may occur if MR data are severely contaminated by irregular breathing patterns. Since irregular breathing can prevent an accurate MR-based 3D respiratory motion model at the end-inspiration phase, the impact of irregular breathing patterns on motion modeling should be evaluated. Similar limitations (accuracy of NRR and impact of irregular breathing patterns on motion modeling) are found in the work of Ren *et al.*, since the positional translation of an internal organ or tumor during respiration was initially determined from uncorrected phase-gated PET images whose artifacts may be considerable due to irregular breathing patterns. Therefore, it is necessary to provide a clinical evidence for the efficiency and robustness of MCIR by investigating the impact of irregular breathing patterns on MCIR and comparing the lesion uptake and detectability of MCIR to that of the current clinical implementation such as PET_Q.

The limitation of this study is that there was no ground truth for PET_Q attenuation correction. For example, CTAC-derived μ -maps could be ground truth as gold standard for evaluating MRAC_{PM-CIRCUS}-derived μ -maps. However, it would be quite demanding to additionally develop a phase-matched CTAC (CTAC_{PM}) method for preparing the gold-standard μ -maps. Furthermore, performing non-rigid registration between phase-matched CT and MR data is prone to errors, especially for the soft tissues in the upper abdomen as well as between arms-up (CT) and arms-down (MR) positions that substantially distort this anatomy, and thus would be challenging to be considered reliable. Instead, we chose to use MRAC_{PM-Default} as sliver standard for the purpose of this study. By comparing MRAC_{PM-CIRCUS} to MRAC_{PM-Default}, we were able to specifically evaluate the effect of accelerating the scan time and highlight any differences due to motion management. We considered MRAC_{PM-Default} as reliable because its implementation is based on the current clinical standard (Dixon-based MRAC) for daily clinical use. However, its limitation is that bone signals with higher attenuation coefficients are not classified correctly. The bone

misclassification of Dixon-based MRAC methods has been previously demonstrated not to make quantitatively meaningful changes for lesions not close to bone (Buerger *et al.*, 2012) such as the liver lesions used for this study. We expect adding bone would affect the MRAC approaches similarly without regard to respiratory phase. A potential limitation of this study is that the empirically chosen values (e.g., $\lambda_{TV}=0.01$ and $\lambda_S=0.01$) might reduce the reproducibility of this study, and thus further efforts might be necessary to optimize the parameters for reproducing this study.

5. Conclusion

We demonstrated that a data acquisition of 30 s achieved phase-matched μ -maps when using specialized CIRCUS data sampling and phase-matched μ -maps improved PET_Q quantification significantly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This project was supported in part by grant from GE Healthcare, NIH/NCI grant R01CA212148, and NIH/NHLBI grant R01HL135490.

References

- Bousse A, Bertolli O, Atkinson D, Arridge S, Ourselin S, Hutton BF and Thielemans K 2016 Maximum-likelihood joint image reconstruction and motion estimation with misaligned attenuation in TOF-PET/CT Phys Med Biol 61 L11–9 [PubMed: 26789205]
- Buerger C, Tsoumpas C, Aitken A, King AP, Schleyer P, Schulz V, Marsden PK and Schaeffter T 2012 Investigation of MR-Based Attenuation Correction and Motion Compensation for Hybrid PET/MR IEEE T Nucl Sci 59 1967–76
- Fayad H, Schmidt H, Kustner T and Visvikis D 2017 4-Dimensional MRI and Attenuation Map Generation in PET/MRI with 4-Dimensional PET-Derived Deformation Matrices: Study of Feasibility for Lung Cancer Applications J Nucl Med 58 833–9 [PubMed: 27738008]
- Geramifar P, Zafarghandi MS, Ghafarian P, Rahmim A and Ay MR 2013 Respiratory-induced errors in tumor quantification and delineation in CT attenuation-corrected PET images: effects of tumor size, tumor location, and respiratory trace: a simulation study using the 4D XCAT phantom Mol Imaging Biol 15 655–65 [PubMed: 23780352]
- Graves EE, Quon A and Loo BW, Jr. 2007 RT_Image: an open-source tool for investigating PET in radiation oncology Technol Cancer Res Treat 6 111–21 [PubMed: 17375973]
- Grimm R, Furst S, Dregely I, Forman C, Hutter JM, Ziegler SI, Nekolla S, Kiefer B, Schwaiger M, Hornegger J and Block T 2013 Self-gated radial MRI for respiratory motion compensation on hybrid PET/MR systems Med Image Comput Comput Assist Interv 16 17–24 [PubMed: 24505739]
- Jiang W, Ong F, Johnson KM, Nagle SK, Hope TA, Lustig M and Larson PEZ 2017 Motion robust high resolution 3D free-breathing pulmonary MRI using dynamic 3D image self-navigator Magn Reson Med
- Kinahan PE, Hasegawa BH and Beyer T 2003 X-ray-based attenuation correction for positron emission tomography/computed tomography scanners Semin Nucl Med 33 166–79 [PubMed: 12931319]
- Kolbitsch C, Neji R, Fenchel M, Mallia A, Marsden P and Schaeffter T 2018 Fully integrated 3D high-resolution multicontrast abdominal PET-MR with high scan efficiency Magn Reson Med 79 900–11 [PubMed: 28503729]

- Liu C, Alessio A, Pierce L, Thielemans K, Wollenweber S, Ganin A and Kinahan P 2010 Quiescent period respiratory gating for PET/CT Med Phys 37 5037–43 [PubMed: 20964223]
- Liu J and Saloner D 2014 Accelerated MRI with CIRCular Cartesian UnderSampling (CIRCUS): a variable density Cartesian sampling strategy for compressed sensing and parallel imaging Quant Imaging Med Surg 4 57–67 [PubMed: 24649436]
- Manber R, Thielemans K, Hutton BF, Wan S, McClelland J, Barnes A, Arridge S, Ourselin S and Atkinson D 2016 Joint PET-MR respiratory motion models for clinical PET motion correction Phys Med Biol 61 6515–30 [PubMed: 27524409]
- Nyflot MJ, Lee TC, Alessio AM, Wollenweber SD, Stearns CW, Bowen SR and Kinahan PE 2015 Impact of CT attenuation correction method on quantitative respiratory-correlated (4D) PET/CT imaging Med Phys 42 110–20 [PubMed: 25563252]
- Polycarpou I, Tsoumpas C, King AP and Marsden PK 2014 Impact of respiratory motion correction and spatial resolution on lesion detection in PET: a simulation study based on real MR dynamic data Phys Med Biol 59 697–713 [PubMed: 24442386]
- Ren S, Jin X, Chan C, Jian Y, Mulnix T, Liu C and Carson RE 2017 Data-driven event-by-event respiratory motion correction using TOF PET list-mode centroid of distribution Phys Med Biol 62 4741–55 [PubMed: 28520558]
- Sureshbabu W and Mawlawi O 2005 PET/CT imaging artifacts J Nucl Med Technol 33 156–61; quiz 63–4 [PubMed: 16145223]
- Tamir JJ, Ong F, Cheng JY, Uecker M and Lustig M 2016 Generalized Magnetic Resonance Image Reconstruction using The Berkeley Advanced Reconstruction Toolbox ISMRM Workshop on Data Sampling and Image Reconstruction
- Uecker M, Tamir JJ, Ong F and Lustig MBART Toolbox for Computational Magnetic Resonance Imaging
- Wollenweber SD, Ambwani S, Lonn AHR, Shanbhag DD, Thiruvankadam S, Kaushik S, Mullick R, Qian H, Delso G and Wiesinger F 2013 Comparison of 4 Class and Continuous Fat/Water Methods for Whole Body, MR-Based PET Attenuation Correction IEEE Trans on Nucl Sci 60 3391–8
- Wurslin C, Schmidt H, Martirosian P, Brendle C, Boss A, Schwenzer NF and Stegger L 2013 Respiratory motion correction in oncologic PET using T1 weighted MR imaging on a simultaneous whole-body PET/MR system J Nucl Med 54 464–71 [PubMed: 23287577]
- Yang J, Yamamoto T, Pollock S, Berger J, Diehn M, Graves EE, Loo BW, Jr. and Keall P J 2016 The impact of audiovisual biofeedback on 4D functional and anatomic imaging: Results of a lung cancer pilot study Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 120 267–72 [PubMed: 27256597]

Figure 1. Simultaneous PET/MRI scan protocol in this study. (a) Phase-Matched MR-based attenuation correction (MRAC_{PM}) data acquisition using CIRcular Cartesian UnderSampling (CIRCUS) k-space sampling (MRAC_{PM-CIRCUS}, 100 s) (b) Phase-Matched MRAC data acquisition (MRAC_{PM-Default}, 100 s) repeating the default two-echo Dixon 3D spoiled-gradient echo imaging (18 s) with raster (“Default”) k-space sampling.

Figure 2. Schematic of phase-matched (PM) MRAC using the CIRCUS strategy (MRAC_{PM-CIRCUS}). (a) Phase-based sorting (30–80% phase) for MRAC data acquired during 100 s in free-breathing; (b) MRAC data acquisition in a pseudo-random, centric-ordered fashion, visualized in k-space with increments of 10 s; (c) Reconstructed MR in-phase at the acquisition times of 10 s, 40 s, 70 s, and 100 s.

Figure 3. Schematic of phase-matched (PM) MRAC using the raster 'Default' sampling (MRAC_{PM-Default}). (a) Weights derived from a respiratory trace for soft gating; (b) MRAC data acquisition during 100 s in free-breathing, visualized in k-space with increments of 10 s; (c) Reconstructed MR in-phase at the acquisition times of 10 s, 40 s, 70 s, and 100 s, (d) Un-Matched (UM) MRAC data without gating. Note that the default sampling fills up the k-space in 18 s but missing k-space data removed during retrospective gating is observed for data acquisition 60 s. In the comparison of PM and UM, retrospective gating reduced motion artifacts and achieved the quiescent period.

Figure 4.

Qualitative comparison of pseudo CT derived from MRAC_{UM}, MRAC_{PM-Default} (100 s) and MRAC_{PM-CIRCUS} (100 s): (a) patient 2, (b) patient 5, (c) patient 6, and (d) patient 8. Both MRAC_{PM-CIRCUS} and MRAC_{PM-Default} achieved the quiescent phase (dashed lines) consistently, reducing motion artifacts observed in MRAC_{UM}. Note that the full 100 s data acquisition was employed for generating phase-matched pseudo CT.

Figure 5.

Boxplots of voxel-wise correlation coefficient (CC, %) between the series of simulated data acquisition (0 – 95 s in increments of 5 s) and the reference full data (100 s) across 17 patients on (a,b) pseudo CT and (c,d) μ -maps for (a,c) MRAC_{PM-Default} and (b,d) MRAC_{PM-CIRUCS}, respectively. Note that the tops and bottoms of each “box” are the 25th and 75th percentiles of the samples, respectively, with the median and outliers (+ sign, $> 1.5 \times$ interquartile range).

Figure 6.

Comparison of pseudo CT image qualities according to data acquisition times (20 s, 40 s, 60 s, 80 s, 100 s) for MRAC_{PM-CIRUCS} (top) and MRAC_{PM-Default} (bottom). The data acquisition of > 60 s is required to achieve an acceptable pseudo CT for MRAC_{PM-Default}.

Figure 7.

Scatterplot of voxel-wise comparison across all patients in the range (0.5 – 30.0 g/mL) of SUV. (a) $MRAC_{PM-CIRCUS}$ (30 s) versus $MRAC_{PM-Default}$ and (b) $MRAC_{UM}$ versus $MRAC_{PM-Default}$. Note that the reference is $MRAC_{PM-Default}$ with the full 100 s data acquisition.

Figure 8.

Boxplot of lesion ($n = 35$) uptake differences (%) for (a) $\text{MRAC}_{\text{PM-CIRCUS}}$ (30 s) and (b) MRAC_{UM} , compared to $\text{MRAC}_{\text{PM-Default}}$. Note that the reference is $\text{MRAC}_{\text{PM-Default}}$ with the full 100 s data acquisition and that the tops and bottoms of each “box” are the 25th and 75th percentiles of the samples, respectively, with the median and outliers (o sign, $> 1.5 \times$ interquartile range).

Figure 9.

Examples of (a) patient 2 and (b) patient 17: (1st row) PET, (2nd row) PET differences, (3rd row) corresponding μ -map and (4th row) μ -map differences for MRAC_{PM-Default} (1st column), MRAC_{UM} (2nd column) and MRAC_{PM-CIRCUS} (3rd column, 30 s). Note that the reference is MRAC_{PM-Default} with the full 100 s data acquisition and that two lesions with SUV_{max} were selected for comparison.

Figure 10.
Fusion of respiratory-resolved four dimensional (4D) PET and 4D MRAC_{PM-CIRCUS}-
derived pseudo CT from end-inspiration to end-expiration phases (a-d).

Table 1.

Summary of lesion (n = 35) uptake differences for MRAC_{PM-CIRCUS} (30 s) and MRAC_{UM}. Note that the reference is MRAC_{PM-Default} with the full 100 s data acquisition. (SUV_{max}: maximum standardized uptake value, SD: Standard Deviation, diff: difference, |diff|: absolute difference).

	Mean±SD	Max	Min
MRAC _{PM-CIRCUS} , SUV _{max} diff	0.0 ± 0.3 (0.1% ± 1.4%)	1.0 (3.2%)	-0.7 (-2.7%)
MRAC _{PM-CIRCUS} , SUV _{max} diff	0.2 ± 0.2 (1.1% ± 0.8%)	1.0 (3.2%)	0.0 (0.0%)
MRAC _{UM} , SUV _{max} diff	0.1 ± 2.4 (0.6% ± 11.4%) *	3.9 (19.8%)	-8.6 (-36.7%)
MRAC _{UM} , SUV _{max} diff	1.3 ± 2.0 (6.5% ± 9.3%) *	8.6 (36.7%)	0.1 (0.1%)

* difference is statistically significant ($P > .05$).