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Preclinical evaluation of MR-attenuation correction versus CT-attenuation correction on a sequential whole-body MR/PET scanner

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Abstract

OBJECTIVES—The application of attenuation correction for combined MR/PET systems is still a major challenge for accurate quantitative PET. CT attenuation correction (CTAC) is the current clinical standard for PET/CT scans. MR, unlike CT, has no direct information about photon attenuation but rather proton densities. On combined MR/PET scanners, MR-based attenuation correction (MRAC) consists of assigning empirical attenuation coefficients to MR signal intensities. The objective of the current study was to evaluate the MRAC implemented on the combined MR/PET scanner versus the CTAC with the same PET data in an animal model.

MATERIALS AND METHODS—MR/PET acquisition was performed using a clinically approved sequential MR/PET scanner (Philips Ingenuity TF). CT and MR/PET images of 20 NZW rabbits were retrospectively analyzed. Animals were positioned on a customized animal bed to avoid movement between CT and MR/PET scanners. PET images from both methods (MRAC and CTAC) were generated. Voxel-by-voxel and region-of-interest (ROI) analyses were performed to determine differences in standardized uptake values (SUV). ROIs were drawn on the coregistered CT images for aorta, liver, kidney, spine and soft tissue (muscle) and superimposed on the PET images.

RESULTS—Voxel-by-voxel comparison of PET showed excellent correlation between MRAC and CTAC SUV values ($R=0.99$, $p<0.0001$). The mean of the difference of SUVs between all respective MRAC and CTAC voxels was -0.94% ($-0.06\pm0.30SD$), confirming slight underestimation of MRAC. The ROI-based comparison similarly showed MRAC SUV values

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were underestimated compared to CTAC. The mean difference between MRAC and CTAC for all ROIs was 10.8% (-0.08 ± 0.06 SD, $R=0.99$, $p<0.0001$) and -9.7% (-0.15 ± 0.12 SD, $R=0.99$, $p<0.0001$) for SUVmean and SUVmax, respectively. The highest differences were found in the spine (SUVmean -26.1% (-0.11)) and areas close to large bones such as the back muscles (SUVmean -16.8% (-0.04)).

CONCLUSIONS—In this study, we have compared MRAC and CTAC methods for PET attenuation correction in an animal model. We have confirmed that the MRAC method implemented on a sequential MR/PET scanner underestimates PET values by less than 10% in most regions, except areas containing or close to large bone structures such as the spine or the back muscles. Bone segmentation is therefore suggested to be included in the MR attenuation map in order to minimize the quantification error of MRAC methods compared to the gold standard CTAC. Further clinical studies need to be carried out to validate the clinical use of MRAC.

INTRODUCTION

Positron Emission Tomography (PET) has the ability to detect picomolar concentrations of a wide range of radiotracers to provide functional imaging. Magnetic resonance imaging (MRI) affords detailed anatomic images with excellent spatial resolution. The evolution of both modalities into powerful, complementary *in vivo* molecular imaging techniques has generated increased interest in the development of combined MR/PET systems. The advent of combined MR/PET systems was first borne out of the desire to have the high spatial resolution and superior soft tissue contrast of MR images directly coregistered to functional PET data.(1) In combined MR/PET systems, the replacement of CT with MR allows superior soft tissue contrast with no ionizing radiation; however, attempting to provide attenuation correction is still a challenge. In addition, detailed anatomical information may be used for motion correction and correction of partial volume effects.(2)

Two clinical whole-body scanners are currently available on the market. The sequential whole-body MR/PET system developed by Philips, utilizes photomultiplier tube (PMT) array detectors, shielded from the MR magnetic field and separated by a distance of 3.0 meters which drops the resulting magnetic field from 3T (30,000G) at the center of the MRI bore to 10G at the center of the PET bore.(3) The simultaneous whole-body MR/PET (Siemens Biograph mMR) incorporates new detector technology based on APD array detectors directly into the housing of the magnet bore.(4) More detailed technical reports of MR/PET system developments can be found in several sources.(2–4)

Despite the recent advances in system development for combined whole-body MR/PET, the most important technical obstacle is the application of attenuation correction. The variable spatial distribution of photon attenuation in tissue must be corrected for in order to permit accurate quantitative evaluation of the final reconstructed PET images. Current MR/PET scanners do not incorporate 511keV transmission sources into the bore of the PET ring and thus the gold standard method of performing attenuation correction by comparing a transmission scan, with the patient in the PET detector ring, to a blank scan, with the patient out of the PET detector ring, is not possible. CT-based attenuation correction (CTAC) is the current clinical standard for correction of PET imaging in PET/CT scans.(5) CT images are directly related to electron density and can be easily transformed into a linear attenuation map at PET energy levels (511keV) for use in PET reconstruction algorithms.(6,7) MRI, in comparison, has no direct information about photon attenuation but rather measures proton densities and magnetic relaxation times. Attenuation correction therefore becomes a nontrivial exercise of deciding how to assign MR signal intensities voxel-by-voxel to empirical photon attenuation coefficients. A growing amount of research has been dedicated to MR-based attenuation correction (MRAC) and its influence on PET image quantification. There are currently two strategies of generating an MR-based attenuation map. The first

strategy involves segmentation of tissue into different classifications and the assignment of empirical photon attenuation coefficient values to each respective tissue classification.(8–16) The second, alternative method to segmentation, has been anatomical atlas registration.(17–19) Segmentation of bone tissues during whole-body acquisitions becomes problematic due to their inherent lack of signal in conventional MR sequences and its similarity to air, which is a large problem in air-bone regions such as the head and lungs. This is in contrast to CT-based attenuation correction, where air and bone are easily distinguished and converted using a bilinear transformation. Ultrashort echo time (UTE) MRI scans have been utilized to add bone segmentation for attenuation correction in the brain but is still in the early development phase.(12) More recently, the combination of UTE and Dixon MRI sequences were used for a 4-segment tissue classification to distinguish fat, water, bone and air also in head and neck imaging.(15) There are many challenges to achieving whole-body MRAC, for instance, the attenuation properties of lungs and benign or malignant tissue growths often vary unpredictably from patient to patient and are difficult to routinely segment.(9) Using the atlas-based strategy, the patient's MR scan is registered to an existing MR atlas. The MR atlas is also registered with a CT atlas that provides *a priori* knowledge of attenuation values. However, there are still questions as to whether a CT or MR atlas accurately represents the anatomy of a specific patient. The critical process in the algorithm is the registration of a specific patient anatomy to an atlas which may fail due to large inconsistencies in global anatomy, such as large malformations within diseased patients.(2,20) Currently, the two clinical MR/PET scanner types available both employ segmentation algorithms to define anatomic regions for assigning attenuation values in MRAC.(9,14,21) However, bone tissue is not currently segmented on either of the two available clinical scanners. More detailed information on segmentation and atlas-based attenuation maps have been discussed.(2,22,23) The objective of the current study was to qualitatively and quantitatively evaluate MRAC implemented on a combined sequential MR/PET scanner versus CTAC with the same PET data in an animal model.

MATERIALS AND METHODS

MR/PET Scanner

MR/PET acquisition was performed using the Philips Ingenuity TF sequential whole-body MR/PET system (Philips Healthcare, Cleveland, OH). The MR/PET system combines the Philips GEMINI TF PET camera and the Philips Achieva 3T X-Series MRI system with a rotating bed that allows accurately registered sequential acquisition of MR and PET images, similar to the standard PET/CT workflow. The PET gantry is placed 3.0 meters from the MR magnet to reduce electromagnetic interference through distance and the use of shielding of the PET detectors (PMTs). PET electronics are housed outside of the MR/PET scanner room to further reduce electromagnetic interference. Further MR/PET system details were presented by Zaidi, *et al.*(3)

Animal Protocol

Twenty New-Zealand White (NZW) male rabbits (mean weight 3.8 ± 0.3 kg) obtained from Covance (Princeton, NJ) were retrospectively analyzed for this study. Animals were injected with 4–5 mCi of either Fluoromisonidazole (^{18}F -FMISO) ($n=12$) or ^{18}F -Fluorodeoxyglucose (^{18}F -FDG) ($n=8$) via the marginal ear vein. During the three hours circulation time, animals were kept in a temperature controlled room to keep the animals warm. Prior to imaging, the animals were anesthetized by an intramuscular injection of ketamine (30 mg/kg; Fort Dodge Animal Health, Fort Dodge, IA, USA) and xylazine (5 mg/kg; Bayer Corporation, USA). A low dose CT scan to provide CT-based attenuation correction was performed immediately prior to sequential MR/PET imaging. To minimize movement between CT and MR/PET scanners, the animals were placed on a half-circle

animal bed developed in-house and comprised of 2mm thick Fiberglass that immobilizes the body of the rabbit in a prone position. Attenuation of the animal bed was not considered in this study. The animal bed did not have an effect on commercial registration algorithms between MR and PET scans. The animal protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the Mount Sinai School of Medicine.

Imaging protocol

PET images were acquired in 3D mode, using time of flight (ToF) information standard on the MR/PET system. PET acquisition was done for 15 minutes at 3 hours after the injection of the radiotracer. In this case, rabbits from the prospective study that were retrospectively analyzed were optimized for vascular inflammation imaging with a 3 hour circulation time. (24) Images were reconstructed into a 128x128x90 matrix with 2x2x2 mm voxel size, using a 3D RAMLA reconstruction algorithm with 3 iterations and 33 subsets and corrections for normalization, dead time, decay, scatter, random coincidences, sensitivity and attenuation. Attenuation correction was provided by both MRAC and CTAC methods on the same PET data sets as explained below to allow comparison of both methods. No dedicated MR coil was present during the MR/PET acquisition in order to allow similar imaging acquisitions for both CT and MRI scanners. Signal reception for MR acquisition was performed using the quadrature body coil. An attenuation template of the MR/PET patient table was included into the final attenuation map during reconstruction, as is standard on the system.

MR Attenuation map

The MRAC method implemented on the Philips whole-body MR/PET system that allows PET attenuation correction is provided by performing a T1-weighted 3D gradient echo sequence with flip angle of 10 degrees, TE 2.2ms, TR 4.2ms, 320mm transverse FOV with 3D slab thickness of 252mm, voxel size 2x2x2mm, and scan duration of 84s.(10) This sequence matches the PET dimensions, provides anatomical information and is used for attenuation correction. The segmentation algorithm to produce the MR map consists of a 3-segment classification: air, lungs and soft tissue. Each tissue is assigned a pre-determined attenuation coefficient. Lungs are segmented from the MR image following a human-like *a priori* model.(10) In this particular study, the lungs are outside the field-of-view and are not segmented. This produces a final body contour segmentation image of the animal with the interior of the animal assigned a predetermined soft-tissue attenuation coefficient (0.095 cm^{-1}) and air attenuation coefficient (0 cm^{-1}). (10,25,26)

CT attenuation map

CT-based attenuation correction (CTAC) was performed by replacing the system standard MR map, used for attenuation correction, with a CT-derived map. Non-contrast low-dose CT images were acquired using a stand-alone CT scanner (256 slice multidetector CT, Philips Healthcare, Brilliance iCT, Cleveland, OH) (voltage 120kV, current 300mA/slice, pitch 0.993, table speed 105.9mm/s, rotation speed 0.75 s/rot, voxel size $0.625 \times 0.625 \times 1 \text{ mm}$, image size $512 \times 512 \times 399$, scan duration 3.76s) prior to the MR/PET acquisition. The CT images were then coregistered to the MR images. Automatic coregistration was performed in SPM8 (SPM, University College London, London, England) using normalized mutual information estimation and $N=128$ bins.(27) Quantification of the accuracy of coregistration was performed by determining five anatomical landmarks, clearly distinguishable in both MR and CT for each ROI (aorta, spine and kidneys) for five rabbits. The distance in the coregistered images between anatomical landmarks was then averaged within each ROI and within all five rabbits examined. The resulting coregistered CT images were then smoothed with a $4 \times 4 \times 4 \text{ mm}$ Gaussian filter to match the PET resolution and then resliced into the PET space. The resliced CT images were then transformed to 511keV attenuation coefficients using a standard bilinear model (6,7) with an in-house program in MATLAB (Mathworks,

Natick, MA). These final CT-derived attenuation maps were then inserted back into the standard MR/PET reconstruction algorithm in place of the MR map, in order to obtain PET reconstructed data with the clinical standard for attenuation correction, CTAC.

Image Analysis

PET data from the 20 rabbits was reconstructed using both the system standard MR-derived attenuation map (MR map) and the CT-derived attenuation map (CT map) inserted into the system PET reconstruction. The resulting MR-based attenuation corrected PET (PET_{MRAC}) and CT-based attenuation corrected PET (PET_{CTAC}) data were then qualitatively and quantitatively evaluated. Quantitative comparison of the differences for both methods was performed by taking the CT-based method as the gold standard. PET images were quantified using the body weight standardized uptake value (SUV).⁽²⁸⁾ Voxel-based and region-based comparisons were performed. The voxel-by-voxel comparison was performed using an in-house program in MATLAB. A correlation plot of all voxels for both methods (MRAC vs. CTAC) and Bland-Altman plots were used to compare differences in PET reconstructed images (PET_{MRAC} versus PET_{CTAC}). For-voxel-by-voxel comparisons, voxels were constrained to only those within the body contour of the rabbit of both the PET_{MRAC} and PET_{CTAC} . Based on mean noise measurements outside the body contour of ten rabbits, voxels with very low uptake dominated by noise (<0.01 SUV) were thresholded from the analysis.

In addition to voxel-by-voxel comparisons, region-based analysis was performed using Osirix (Osirix Imaging software, Pixmeo, Geneva, Switzerland) to determine differences in attenuation coefficients and SUV within specific tissue regions. Six regions of interest (ROI) were defined: aorta, liver, kidneys (left and right), spine and soft tissue (back muscle). ROIs were traced manually in the axial view of the coregistered CT images for each body part. The left and right kidneys were traced outlining the whole kidney cross section in each axial slice with an average of 20 slices per kidney. The liver was traced in its entirety, as well, with ROIs outlining the whole liver cross section in each axial slice with an average of 24 slices to cover the liver. The aorta, spine and soft tissue were each traced for 15 axial slices placed near the kidneys to ensure similar axial slices were analyzed. For the spine and aorta, outlines of the cross sections of both anatomies in each slice were traced. The back muscles were traced in a central region of soft tissue next the spine ensuring only soft tissue was traced. These were then superimposed on the CT attenuation map, PET_{MRAC} and PET_{CTAC} images. No partial volume correction was performed for this study. Mean CT attenuation coefficient, standard deviation and absolute and percent differences compared to MR attenuation coefficient were calculated for each ROI in the CT attenuation map. SUV mean and SUV maximum were calculated for each ROI in the PET_{MRAC} and PET_{CTAC} images. Similarly to the voxel-based comparison, correlation plots and Bland-Altman plots were used to compare SUV mean and max. Additional comparison was done to evaluate the possible impact of the radiotracer injected, FMISO and FDG, in the observed differences of both methods.

Statistical analyses to compare the results of both methods (MRAC and CTAC) and differences in CT and MR attenuation coefficients were done using SPSS software (SPSS, Chicago, IL). Pearson's correlation and paired t-test were evaluated to identify correlation and significant differences between both methods respectively. Statistical significance was considered for $p < 0.01$.

RESULTS

Figure 1 shows an example of the accuracy the coregistration reached by using the customized bed to minimize animal movement. Table 1 shows a summary of coregistration

accuracy measured using anatomical landmarks. Figure 2A–C displays coronal plane comparisons of the CT-derived map, the MR map, and a comparison of their percent differences in attenuation coefficient values, respectively. Figure 2D–F displays the same coronal plane comparisons between PET_{CTAC} and PET_{MRAC} reconstructed data sets and percent difference in SUV for each method, respectively.

Voxel-by-voxel comparison

Voxel-by-voxel comparison of PET values for all rabbits showed excellent correlation between MRAC and CTAC SUV values ($R=0.99$, $p<0.0001$) (Fig 3A). The Bland-Altman plot showed that the mean of the difference of SUVs between MRAC and CTAC voxels for all rabbits was -0.94% ($-0.06\pm0.30SD$) (Fig 3B), confirming a slight underestimation of the MRAC method versus the gold standard CTAC.

Region-of-interest comparison

Figure 4 shows an example of the ROIs drawn on the coregistered CT images. Table 2 provides a summary of MR and CT attenuation coefficient values for each ROI analyzed. Significant differences were found in the mean CT attenuation coefficients, as compared to assigned MR attenuation coefficients, in all ROIs except for the right kidney ($p=0.15$). The three highest percent and absolute differences in attenuation coefficients were the spine -12.4% (-0.01344 cm^{-1} , $p<0.0001$), aorta 5.5% (0.00497 cm^{-1} , $p<0.0001$), and soft tissue -4.2% (-0.00419 cm^{-1} , $p<0.0001$). Table 3 provides a summary of the calculations of mean, minimum, maximum and standard deviations for PET_{MRAC} versus PET_{CTAC} in the ROIs included. The ROI-based comparison showed that MRAC SUV values were underestimated compared to CTAC SUV values, as shown in Figure 5. The mean difference between MRAC and CTAC for all ROIs was -10.8% ($-0.08\pm0.06SD$, $R=0.99$, $p<0.0001$) for SUV_{mean} (Fig 5A/C) and -9.7% ($-0.15\pm0.12SD$, $R=0.99$, $p<0.0001$) (Fig 5B/D) for SUV_{max}. The highest differences were found in areas containing or close to large bone structures, such as the spine (SUV_{mean} -26.1% (-0.11), SUV_{max} -23.6% (-0.17)) and the back muscle (SUV_{mean} -16.8% (-0.04), SUV_{max} -15.5% (-0.07)).

Table 4 provides a summary of the calculations of percent differences seen for all rabbits. The highest percent differences, with respect to tracer injected, were in the spine (FDG, SUV_{mean} -21.7% (-0.15), SUV_{max} -19.5% (-0.26); FMISO, SUV_{mean} -35.5% (-0.08), SUV_{max} -32.2% (-0.11)) and the back muscles (FDG, SUV_{mean} -17.7% (-0.05), SUV_{max} -17.4% (-0.12); FMISO, SUV_{mean} -15.8% (-0.02), SUV_{max} -12.5% (-0.04)). Additionally, in the aorta of rabbits injected with FMISO, there was a large underestimation of MRAC versus CTAC (FMISO, SUV_{mean} -21.2% (-0.03), SUV_{max} -17.4% (-0.04)); however, differences for FDG remained relatively low (FDG, SUV_{mean} -4.3% (-0.02), SUV_{max} 2.6% (-0.01)).

Table 5 provides a summary of values of PET_{CTAC} and PET_{MRAC} SUV_{mean} and SUV_{max} and absolute differences for each ROI and all ROIs combined. Within each ROI category, SUV_{mean} and SUV_{max} and absolute differences are divided into comparisons for all rabbits ($n=20$), FDG injected rabbits ($n=8$) and FMISO injected rabbits ($n=12$).

DISCUSSION

The current study shows a comparison of the same set of PET data reconstructed with MRAC and CTAC methods. To minimize movement between CT and MR/PET scanners, the animals were placed in a prone position on a customized animal bed developed in-house. Using this method, we were able to facilitate accurate coregistration (Fig 1) (Table 1) and minimize quantification errors from misregistration. Mean misregistration between CT and

MR/PET was less than 2mm, which is 2.5 times smaller than the actual PET resolution of the scanner. The CT attenuation coefficients are also filtered with a 4mm Gaussian filter to match PET resolution. Therefore, the effects of misregistration have very little impact in the final PET quantification. MRAC demonstrates a strong overall voxel-by-voxel correlation ($R=0.99$, $p<0.0001$) of SUVs in comparison to CTAC with a slight general underestimation of MRAC voxels. This is confirmed by a Bland-Altman plot, showing an average underestimation of MRAC of -0.94% ($-0.06\pm 0.30SD$) on SUVs (Fig 3B). In order to determine what regional differences might be most affected by the use of MRAC, analysis was performed on six ROIs, aorta, liver, left and right kidney, spine and soft tissue (back muscle) (Fig. 4). In general, the MRAC method underestimates the PET SUVs in comparison with the gold-standard CTAC, with mean difference for all ROIs of -10.8% ($p<0.0001$) and -9.7% ($p<0.0001$) for SUVmean and SUVmax, respectively (Figure 5). As expected, the highest differences were found in the spine (SUVmean -26.1% (-0.11), SUVmax -23.6% (-0.17) and areas close to large bones such as the back muscles (SUVmean -16.8% (-0.04), SUVmax -15.5% (-0.07)), likely due to the lack of bone segmentation and differences in CT soft tissue attenuation coefficient average in the back muscles (0.099 cm^{-1}) versus the MR attenuation coefficient (0.095 cm^{-1}). The relatively small underestimation of the voxel-by-voxel compared to higher underestimation in the ROI-based analysis may be due to the inclusion of some regions of overestimation farther away from bone structures as was seen in previous studies simulating bone set to soft tissue or ignoring adipose tissue.(13,22) As mentioned previously, significant differences were found in the mean CT attenuation coefficients as compared to assigned MR attenuation coefficients in all ROIs except for the right kidney ($p=0.15$). The three highest percent and absolute differences in attenuation coefficients (Spine -12.4% (-0.01344 cm^{-1} , $p<0.0001$), Aorta 5.5% (0.00497 cm^{-1} , $p<0.0001$), Soft Tissue -4.2% (-0.00419 cm^{-1} , $p<0.0001$)) were also the three highest percent differences in SUVmean calculation when comparing all twenty rabbits (Spine -26.1% , Aorta -10.4% , Soft Tissue -16.8%).

In addition to ROI based analysis, differences were analyzed according to the injected radiotracer (FDG or FMISO) to calculate tracer dependent ROI differences. The highest tracer dependent differences were in the spine ((FDG, SUVmean -21.7% (-0.15), SUVmax -19.5% (-0.26); FMISO, SUVmean -35.5% (-0.08), SUVmax -32.2% (-0.11)) and the back muscles (FDG, SUVmean -17.7% (-0.05), SUVmax -17.4% (-0.12); FMISO, SUVmean -15.8% (-0.02), SUVmax -12.5% (-0.04)). The aorta of rabbits injected with FMISO showed a large underestimation of MRAC versus CTAC (FMISO, SUVmean -21.2% (-0.03), SUVmax -17.4% (-0.04)); however, differences for FDG remained relatively low (FDG, SUVmean -4.3% (-0.02), SUVmax 2.6% (-0.01)). The large percent differences seen in tracer dependent comparisons for FMISO versus FDG are due to the relatively low tracer uptake associated with FMISO as compared with that of FDG (Table 5). Calculating the percentage differences in such low FMISO uptake regions such as the aorta, spine and soft tissue naturally leads to large differences.

The global SUV ROI results reflect slightly higher underestimation in terms of percent differences as compared to other previous studies.(9–11,13) In their study, Martinez-Moller, *et al*, found that osseous lesions were underestimated by 8.0% when not segmenting bone in the attenuation map. However, this study was done in humans and using segmentation for fat and soft tissue in addition to lungs and air. Additionally, the MRI-derived attenuation map was generated from setting bone in an acquired CT scan to soft tissue as proof of principle rather than acquiring and segmenting an MRI of the patient. Assigned soft tissue values also differ slightly from our study (0.10 cm^{-1}), which is higher than the value used in ours (0.095 cm^{-1}).(9) The underestimation of osseous lesions was determined to be clinically insignificant by an observer in the study. Steinberg, *et al*, using a three-region segmentation of lung, soft tissue and air in beagles showed an underestimation in the spine

of 14% with slightly different soft tissue values (0.098 cm^{-1}), again, higher than in our case and acquisition was performed on PET/CT and MR(11). In a simulation study of segmented human attenuation maps, Keereman, *et al*, showed several lesions were significantly underestimated when not taking spongy or cortical bone into account in whole-body MR/PET simulations.(13) In the spine, underestimation of 11.7% and 10.8% was seen in two lesions when replacing spongy bone with soft tissue and underestimation of 15.6% and 17.5% was seen in the same two lesions in the spine when replacing cortical bone with soft tissue. In addition, replacing spongy bone with soft tissue underestimated a lesion in the pelvis by 13.1%. Hu, *et al*, in a study in humans using the same three-region segmentation method implemented on the Philips MR/PET scanner but using a PET/CT and a separated MRI scanner, reported underestimated lesions of 7.6% in the spine and 11.7% in the pelvis. It has been suggested that segmentation of bone will only be necessary when quantifying lesions within a region of bone.(11) We have shown that in this animal model the underestimation of soft tissue near the spine (back muscles) was 17%. Other groups have also shown that larger errors could occur when ignoring bone when segmenting CT for CTAC. Hoffman, *et al*, reconstructed PET images using an original CT and the same CT with bone set to soft tissue attenuation values and found underestimation of up to 60% in the spine and overestimation in surrounding tissue of up to 10%. (22) These results encourage the use of bone segmentation to be included on MR attenuation maps, not only for quantification in bone but of areas near high bone volume, in order to minimize quantification errors of MRAC methods compared to CTAC. Ultrashort Echo Time (UTE) sequences have been developed and implemented successfully in head and neck and imaging. (12,15) Acquisition time for UTE sequences can be lengthy and has not yet been accomplished for whole-body imaging but is nonetheless promising in reducing quantification errors. Due to its proximity to the spine, it is worth noting the underestimation of the aorta in our study was near the limit of clinically accepted differences for SUVmean (-10.4%) but well under the limit for SUV max (-7.6%). Taking a close look at the differences in the FMISO group, the low uptake in the aorta of rabbits led to a larger percentage underestimation of MRAC versus CTAC (SUVmean -21.2% , SUVmax -17.4%), while, differences for the FDG group remained relatively low (SUVmean -4.3% , SUVmax -2.6%). It is important to note that the average underestimation in the aorta is increased by the high underestimation calculations due to very low FMISO tracer uptake.

In the context of these observations, it is clear that there have been a wide range of underestimation values reported (7–60%) in the literature when ignoring bone in MRAC methods. The animal model used may have an influence on the degree of underestimation of SUV when bone is replaced with soft tissue because of the percentage of total body volume that represents the skeleton.(11,13) In addition, iterative reconstruction methods could lead to differences in final PET quantification values; however, up to date, there has not been any work provided on the effect of different iterative reconstruction protocols on the final SUV values. In our study, given that the same PET data was reconstructed using identical reconstruction parameters, with the only change being the use of a CT map versus an MR map, we can infer that general underestimation in SUVs for each voxel were caused by the use of an MR-based attenuation map versus the current clinical standard CT-based attenuation map. This study does not provide work for any bone segmentation, for inclusion within the MR-based attenuation map, but it would be of interest in the future to compare quantification with and without bone segmentation for MRAC as compared to CTAC. Due to the retrospective nature of the study, the acquisition protocol was not optimized to include the head and neck, lungs and heart of the rabbits. The protocol was performed using one bed position from the diaphragm to the iliac bifurcation. Prospective studies are currently underway to address additional regions-of-interest.

We also observed in this study a difference in underestimation in the kidneys despite the fact that they are both estimated as soft tissue in the MR map: left (−9.8% SUVmean) and right (−6.2% SUVmean). Differences in the mean CT attenuation coefficients as compared to assigned MR attenuation coefficients for the left kidney were significant (−0.7% (−0.00063 cm^{−1}, p<0.0001) although differences in the right kidney were insignificant (0.2% (0.00020 cm^{−1}, p=0.15). In addition, upon further inspection, it could be observed that the left kidney is always surrounded by more fat, which is a less dense tissue than normal soft tissue, than the right kidney (Fig 1). Such differences in attenuation coefficients may also explain the final differences observed in the PET reconstructed images between the MRAC and the CTAC methods. MRAC methods using the Dixon sequence, to distinguish fat and soft tissue, have been successful and may be important in soft tissue pathologies in the abdomen (near the kidneys and liver) and head and neck regions where fat is more abundant. (9,15,21,29)

Implementation of a customized animal bed minimized errors in coregistration (Table 1). As mentioned previously, the misregistration between CT and MR/PET was 2.5 times smaller than the actual PET resolution of the scanner. After application of a Gaussian filter to the CT attenuation coefficients there is very little impact of misregistration in the final PET quantification. However, there may still be some small quantification differences in the final PET from breathing artefacts (near the body surface) and air pocket movement coinciding with peristaltic movements in the bowels between CT and MR acquisition and also between MR and PET acquisition. Due to the fact that PET acquisition was on free-breath cycles for long periods of time, accurate non-rigid registration will not add major changes, as the CT reflects one breath position of the breath cycle but not the averaging effect of the free-breathing cycle during PET acquisition. In fact for this reason, CT may not be the perfect clinical standard for attenuation correction. Since the MR sequence is an averaged acquisition over a longer period of time compared to CT (84s vs. 3.76s) motion during the free-breathing cycle and peristaltic motion is averaged out in a more similar fashion to the free-breathing PET acquisition. Simultaneous MR and PET acquisitions, where cardiac and respiratory gating of both acquisitions can be performed, may provide superior attenuation correction versus PET/CT. In our case the interior portion of the rabbit was segmented as only soft tissue so these artefacts would be most prominent at the contour boundary of soft tissue and air where misclassification of air or soft tissue may occur depending on when during the breathing cycle the CT was captured. Coils were not present during PET acquisition to avoid any attenuation effects and avoid increasing errors on the PET signal. However, further studies of the effects of coils in the field of view during PET acquisition need to be done to fully validate the use of MR/PET imaging. Such studies are currently under development.

In this study, we have addressed the reconstruction of the same set of PET data using both the clinically approved MR-based attenuation correction (MRAC) method implemented on the Philips MR/PET scanner and CT-based attenuation correction (CTAC) method in an animal model using NZW rabbits. We have examined their quantitative effects on the final MR/PET images. We have confirmed that the MRAC method implemented on this MR/PET scanner underestimates PET values by less than 10% in most regions, except areas containing or close to large bone structures such as the spine or back muscles. Including bone segmentation in MRAC methods would minimize the quantification errors of such areas in comparison to the gold standard CTAC. However, further clinical studies need to be carried out to validate the clinical implementation of MRAC in patients and to address whether the differences between both methods become clinically significant. Despite the underestimation of PET SUVs with the MRAC employed on the sequential MR/PET, the two-segment classification of air and soft tissue implemented is reasonable in regions distant from bone, but becomes inaccurate near bone and in regions with low activity uptake.

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Figure 1.

Example of A) CT image B) MR image and C) coregistration of CT and MR images. The use of the customized animal bed minimizes non-rigid movement between the scans and facilitates the automatic coregistration. Arrows demonstrate that the left kidney is surrounded by fat in both the foot and head directions while the right kidney is bounded by the liver, a more dense tissue than fat, in the head direction.

Figure 2.

Representative images of A) CT map B) MR map C) percent difference between MR and CT maps. Table 1 summarizes the analysis of attenuation coefficient differences in the CT and MR maps. D) CT-based attenuation correction PET E) MR-based attenuation correction PET F) percent difference between MR-based attenuation correction PET and CT-based attenuation correction PET.

Figure 3.

Voxel by voxel comparison of MR-based attenuation correction vs. CT-based attenuation correction methods. Voxels with very low uptake dominated by noise (<0.01 SUV) were thresholded from the analysis. A) Correlation plot showing MR-based attenuation correction PET versus CT-based attenuation correction PET of SUVs from all rabbits. The red line shows the linear regression fit of the data, showing a slight underestimation from the one-to-one correspondence (yellow line) of MR-based attenuation correction vs. CT-based attenuation correction. B) Bland-Altman plot of SUV measurements. The red dashed lines represent the 95% confidence interval (95% CI). The yellow dashed line represents the mean of the differences between MR-based attenuation correction PET and CT-based attenuation correction PET.

Figure 4. Example of the anatomical regions of interest (ROIs) drawn on the coregistered CT images: aorta (orange), liver (brown), left kidney (light blue), right kidney (green), spine (dark blue) and soft tissue (back muscles) (red).

Figure 5.

Plots showing MR-based attenuation correction PET versus CT-based attenuation correction PET correlation for the six regions of interest for A) SUV mean B) SUV max. The dashed line shows the linear regression fit of the data between MR-based attenuation correction PET to CT-based attenuation correction PET, confirming the slight underestimation from the one-to-one correspondence (solid line) as observed in the voxel-by-voxel case. C,D) Bland-Altman plots for the six regions of interest for SUV mean (C) and SUV max (D). The red dashed lines represent the 95% confidence interval (95% CI). The blue dashed line represents the mean of the differences between MR-based attenuation correction PET versus CT-based attenuation correction PET.

Table 1

Summary of coregistration accuracy using anatomical landmarks. Within each rabbit (n=5), five anatomical landmarks, clearly distinguishable in both MR and CT, were marked in each ROI. The distance in the coregistered images between anatomical landmarks was then average within each ROI and within all five rabbits examined.

Distance (mm)	SPINE	AORTA	KIDNEY	ALL
Mean	1.16	1.40	1.73	1.43
Min	0.18	0.02	0.19	0.02
Max	1.97	2.79	3.81	3.81
Std Dev	0.52	0.80	0.99	0.82

Table 2

Summary of MR and CT attenuation coefficient values for each ROJ analyzed. Within each ROJ category, mean MR attenuation coefficient, mean CT attenuation coefficient, CT attenuation coefficient standard deviation, absolute difference and percent difference are compared for all rabbits (n=20).

ROI	MR attenuation coefficient (cm ⁻¹)	Mean CT attenuation coefficient (cm ⁻¹)	CT attenuation coefficient std dev (cm ⁻¹)	absolute difference (cm ⁻¹)	percent difference (%)	p
Aorta	0.09500	0.09003	0.00422	0.00497	5.5	<0.0001
Liver	0.09500	0.09764	0.00123	-0.00264	-2.7	<0.0001
Left Kidney	0.09500	0.09563	0.00308	-0.00063	-0.7	<0.0001
Right Kidney	0.09500	0.09480	0.00318	0.00020	0.2	0.15
Spine	0.09500	0.10844	0.00650	-0.01344	-12.4	<0.0001
Soft Tissue	0.09500	0.09919	0.00089	-0.00419	-4.2	<0.0001

Table 3

Summary of SUV mean, minimum and maximum values of regions of interest in PET images for both PET_{MRAC} to PET_{CTAC}

	Mean SUV $\pm$ Standard Deviation (SUV _{min} , SUV _{max})		
ROI	PET _{CTAC}	PET _{MRAC}	p
AORTA	0.30 $\pm$ 0.22 (0.25, 0.37)	0.27 $\pm$ 0.22 (0.22, 0.35)	<0.0001
LIVER	1.06 $\pm$ 0.68 (0.54, 1.40)	0.95 $\pm$ 0.62 (0.47, 1.27)	<0.0001
LEFT KIDNEY	1.24 $\pm$ 0.55 (0.34, 3.02)	1.12 $\pm$ 0.48 (0.31, 2.47)	<0.0001
RIGHT KIDNEY	1.22 $\pm$ 0.56 (0.31, 3.11)	1.14 $\pm$ 0.53 (0.30, 2.91)	<0.0001
SPINE	0.42 $\pm$ 0.30 (0.21, 0.71)	0.31 $\pm$ 0.25 (0.15, 0.54)	<0.0001
SOFT TISSUE	0.19 $\pm$ 0.11 (0.13, 0.45)	0.16 $\pm$ 0.10 (0.11, 0.38)	<0.0001

Table 4

Summary of percent differences for each **ROI** and all ROIs combined. Within each **ROI** category, percent differences are divided into comparisons for all rabbits (n=20), FDG injected rabbits (n=8) and FMISO injected rabbits (n=12).

	Rabbits	Percent Difference SUVmean	Percent Difference SUVmax
ALL ROIs	ALL	-10.8	-9.7
	FDG	-10.6	-10.4
	FMISO	-11.0	-9.2
Aorta	ALL	-10.4	-7.6
	FDG	-4.3	-2.6
	FMISO	-21.2	-17.4
Liver	ALL	-10.4	-9.3
	FDG	-9.5	-8.7
	FMISO	-12.1	-10.3
Left Kidney	ALL	-9.8	-9.5
	FDG	-10.2	-10.1
	FMISO	-9.5	-9.1
Right Kidney	ALL	-6.2	-6.4
	FDG	-7.2	-7.5
	FMISO	-5.5	-5.8
Spine	ALL	-26.1	-23.6
	FDG	-21.7	-19.5
	FMISO	-35.5	-32.2
Soft Tissue	ALL	-16.8	-15.5
	FDG	-17.7	-17.4
	FMISO	-15.8	-12.5

Table 5

Summary of radiotracer dependent values of PET_{CTAC} and PET_{MRAC} SUVmean and SUVmax and absolute differences for each ROI and all ROIs combined. Within each ROI category, SUVmean and SUVmax and absolute differences are divided into comparisons for all rabbits (n=20), FDG injected rabbits (n=8) and FMISO injected rabbits (n=12).

	Rabbits	Average SUVmean		Absolute Difference SUVmean		Average SUVmax		Absolute Difference SUVmax	
		PET _{CTAC}	PET _{MRAC}			PET _{MRAC}	PET _{MRAC}		
ALL ROIs	ALL	0.74	0.66	-0.08		1.51	1.37	-0.14	
	FDG	0.94	0.84	-0.10		1.68	1.51	-0.17	
	FMISO	0.61	0.54	-0.07		1.40	1.27	-0.13	
Aorta	ALL	0.30	0.27	-0.03		0.37	0.35	-0.02	
	FDG	0.49	0.47	-0.02		0.62	0.61	-0.01	
	FMISO	0.18	0.15	-0.03		0.21	0.17	-0.04	
Liver	ALL	1.07	0.95	-0.12		1.40	1.27	-0.13	
	FDG	1.76	1.59	-0.17		2.19	2.00	-0.19	
	FMISO	0.60	0.53	-0.07		0.87	0.78	-0.11	
Left Kidney	ALL	1.24	1.12	-0.12		3.02	2.74	-0.28	
	FDG	1.26	1.13	-0.13		2.75	2.47	-0.28	
	FMISO	1.23	1.12	-0.11		3.21	2.91	-0.30	
Right Kidney	ALL	1.22	1.14	-0.08		3.11	2.91	-0.20	
	FDG	1.16	1.08	-0.08		2.54	2.34	-0.20	
	FMISO	1.25	1.19	-0.06		3.50	3.30	-0.20	
Spine	ALL	0.42	0.31	-0.11		0.71	0.54	-0.17	
	FDG	0.72	0.57	-0.15		1.31	1.05	-0.26	
	FMISO	0.22	0.14	-0.08		0.31	0.20	-0.11	
Soft Tissue	ALL	0.20	0.16	-0.04		0.45	0.38	-0.07	
	FDG	0.25	0.20	-0.05		0.70	0.58	-0.12	
	FMISO	0.16	0.14	-0.02		0.29	0.25	-0.04	