

The Effect of Including Bone in DIXON-based Attenuation Correction for ^{18}F -fluciclovine PET/MRI of Prostate Cancer

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The objective of this study was to evaluate the effect of including bone in DIXON-based attenuation correction for ^{18}F -fluciclovine Positron Emission Tomography (PET) / Magnetic Resonance Imaging (MRI) of primary and recurrent prostate cancer.

Methods: ^{18}F -fluciclovine PET data from two PET/MRI studies – one for staging of high-risk prostate cancer (28 patients) and one for diagnosis of recurrent prostate cancer (81 patients) – were reconstructed with a 4-compartment (reference) and 5-compartment attenuation map. In the latter, continuous linear attenuation coefficients for bone were included by co-registration with an atlas. The maximum and mean 50% isocontour standardized uptake values (SUV_{max} and SUV_{iso} , respectively) of primary, locally recurrent, and metastatic lesions were compared between the two reconstruction methods using linear mixed-effects models. In addition, mean SUVs were obtained from bone marrow in the third lumbar vertebra (L3) to investigate the effect of including bone attenuation on lesion-to-bone marrow SUV ratios (SUVR_{max} and SUVR_{iso} ; recurrence study only). The 5-compartment attenuation maps were visually compared to the in-phase DIXON MR images for evaluation of bone registration errors near the lesions. P-values < 0.05 were considered significant.

Results: Sixty-two (62) lesions from 39 patients were evaluated. Bone registration errors were found near 19 (31%) of these lesions. In the remaining 8 primary prostate tumors, 7 locally recurrent lesions, and 28 lymph node metastases without bone registration errors, using the 5-compartment attenuation map was associated with small but significant increases in SUV_{max} [2.5%; 95% confidence interval (CI) 2.0%-3.0%; $p < 0.001$] and SUV_{iso} (2.5%; 95%

CI 1.9%-3.0%; $p < 0.001$), but not $SUVR_{max}$ (0.2%; 95% CI -0.5%-0.9%; $p = 0.604$) and $SUVR_{iso}$ (0.2%; 95% CI -0.6%-1.0%; $p = 0.581$), in comparison to the 4-compartment attenuation map. **Conclusion:** The investigated method for atlas-based inclusion of bone in ^{18}F -fluciclovine PET/MRI attenuation correction has only a small effect on the SUVs of soft-tissue prostate cancer lesions, and no effect on their lesion-to-bone marrow SUVs when using signal from L3 as a reference. The attenuation maps should always be checked for registration artefacts for lesions in or close to the bones.

INTRODUCTION

Medical imaging plays an increasingly important role in the management of prostate cancer, which is the most frequently detected type of cancer in men in developed countries (1). Multiparametric Magnetic Resonance Imaging (MRI), i.e. the combination of anatomical T2-weighted imaging and functional diffusion-weighted and dynamic contrast-enhanced imaging, is currently recommended for staging of primary prostate cancer (2), while molecular imaging with Positron Emission Tomography (PET) has shown promise for the detection of primary and recurrent prostate cancer (3-7). Since the introduction of integrated PET/MRI scanners, these complementary data sets can be simultaneously acquired, thereby potentially improving the diagnostic accuracy in comparison to either modality alone (3,4,8,9).

In contrast to computed tomography (CT), however, MRI does not provide an estimate of the electron densities that determine the attenuation of the 511 keV annihilation photons in the patient's body. Correction for attenuation, which is required for quantitatively accurate PET imaging, is therefore technically challenging on a PET/MRI system. In current clinical practice, fast T1-weighted or DIXON MR scans are used to create an attenuation map with fixed linear attenuation coefficients for three (soft tissue, lung, background air) (10) or four segmented compartments (soft tissue, fat, lung, and background air) (11), respectively. In both cases, the linear attenuation coefficient of soft tissue is assigned to bones, which typically leads to an underestimation of the standardized uptake values (SUVs) in lesions in and close to

bony structures (12,13). In a simulation study with known ground truth, Keeremans et al estimated the underestimation of SUVs in the prostate region to be around -4% (13).

Paulus et al recently presented a method to solve this issue, by including continuous bone linear attenuation coefficients in the DIXON-based attenuation map, based on co-registration of the DIXON images with an atlas of MR and CT pairs of the major bones in the body (14). This method, which is currently implemented on Siemens mMR PET/MRI scanners, was reported to substantially reduce the underestimation of SUV in bone lesions (14,15) and soft tissue lesions in the brain (16). The effect on the SUV in soft-tissue lesions in the body, on the other hand, was particularly small (14,15). However, the latter results were derived from ^{18}F -FDG PET/MRI data – a radiotracer which is not useful in the context of prostate cancer. Consequently, the effect of model-based inclusion of bone attenuation values has not been assessed for clinical prostate cancer imaging. Incorrect bone attenuation values could affect the quantitative accuracy of prostate (bed), lymph node, and bone lesion SUVs in the bone-dense pelvis, as well as obscure the qualitative comparison with uptake in spinal bone marrow, which is a commonly used evaluation criterion in clinical practice (17).

The objective of this work was therefore to investigate the effect of including bone in DIXON-based attenuation correction for PET/MRI of primary and recurrent prostate cancer. For this purpose, we retrospectively analyzed a cohort of patients examined with ^{18}F -fluciclovine [anti-1-amino-3- ^{18}F -fluorocyclobutane-1-carboxylic acid

(¹⁸F-FACBC)] PET/MRI, which is a Federal Drug Administration and European Medicines Agency approved radiotracer for use in recurrent prostate cancer.

MATERIALS AND METHODS

Patients

In this work, we retrospectively reconstructed and analyzed ^{18}F -fluciclovine PET/MRI data from two prospective studies performed at our institution (St. Olavs Hospital, Trondheim University Hospital). The first study, which will be referred to as the staging study, included patients classified as high-risk according to modified D'Amico criteria (PSA > 20 ng/ml and/or clinical stage \geq cT3a and/or Gleason score \geq 8) to investigate the merit of combined ^{18}F -fluciclovine PET/MRI for loco-regional staging of primary prostate cancer (ClinicalTrials.gov; identifier NCT02076503) (18). The second study, which will be referred to as the recurrence study, included patients that fulfilled the European Association of Urology criteria for biochemical relapse following radical treatment (two consecutive measurements with PSA \geq 0.2 ng/ml following radical prostatectomy or PSA \geq 2.0 ng/ml above the nadir following definitive radiotherapy) to investigate the diagnostic accuracy of combined ^{18}F -fluciclovine PET/MRI for detection of recurrent prostate cancer (ClinicalTrials.gov; identifier NCT02562131). Both studies were approved by our institution and the Regional Committee for Medical and Health Research Ethics Central Norway. All patients signed a written informed consent before enrollment.

Imaging and Reconstruction

Both imaging studies were performed on a 3 T Biograph mMR PET/MRI scanner (Siemens Healthcare GmbH, Erlangen, Germany). All PET images were offline

reconstructed (Siemens HDPET, 3 iterations, 21 subsets, 4 mm full width at half maximum Gaussian filter) using 4-compartment (soft tissue, fat, lung, and background air) and 5-compartment (soft tissue, fat, lung, background air, and bone) attenuation maps. Both attenuation maps were created from the DIXON MR series (1st echo time 1.23 ms, 2nd echo time 2.46 ms, repetition time 3.6 ms, voxel size $4.1 \times 2.6 \times 3.1 \text{ mm}^3$, field of view $500 \times 329 \times 400 \text{ mm}^3$) using the dedicated tool for offline generation of attenuation maps available on the software platform (*syngo* MR E11P, Siemens Healthcare GmbH) of the scanner. In short, for the 4-compartment attenuation map, soft tissue, fat, lung, and air voxels were automatically segmented and assigned fixed 511 keV linear attenuation coefficients of 0.1000, 0.0854, 0.0224, and 0 cm^{-1} , respectively. For the 5-compartment attenuation map, continuous bone linear attenuation coefficients were superimposed on the 4-compartment attenuation map by co-registration of the DIXON series to an atlas of MR and CT pairs of the major bones in the body, as described in more detail by Paulus et al (14).

In the staging study, the PET images for evaluation of lymph node metastases covered the lymph nodes from the pelvic floor up to the ureteral crossing of the common iliac vessels, as previously described (8,19), and were reconstructed from the counts in a time-window 5 – 10 minutes post tracer injection. The PET images for evaluation of prostate tumors were centered on the prostate and were reconstructed from the counts in a time-window 33 – 38 minutes post tracer-injection. In the recurrence study, PET images were acquired in four consecutive, partly overlapping,

bed positions covering the patient from the lower pelvis to the neck. Acquisition lasted 4 minutes per bed position and was started approximately 5 minutes post tracer-injection.

Volumes-of-interest

For the patients in the staging study, volumes-of-interest (VOIs) of primary prostate tumors and pelvic lymph node metastases were considered. The prostate tumor VOIs were defined as the 50% isocontour of the maximum SUV in the corresponding histology-based VOIs, which were available from a previous study (19). The lymph nodes classified as malignant by a nuclear medicine physician were retrospectively identified on the PET images reconstructed with the 4-compartment attenuation map. VOIs were defined as the 50% isocontour of the maximum SUV in a sphere encompassing the entire lymph node. The latter approach was also used to define the VOIs of recurrent prostate tumors, pelvic lymph nodes, para-aortic lymph nodes, and bone lesions in the recurrence study. In all cases, isocontouring was performed separately on the PET images reconstructed with the 4 and 5-compartment attenuation maps. In addition, spherical VOIs (8 mm radius) were placed in the third lumbar vertebra (L3) of the patients in the recurrence study to calculate lesion-to-bone marrow SUVs.

The maximum and mean SUV (SUV_{max} and SUV_{iso} , respectively) were obtained for each of the lesion VOIs. For the patients in the recurrence study, the mean SUVs of the bone marrow VOI (SUV^{bm}) were obtained and maximum and mean lesion-to-bone

marrow SUV ratios (SUVRs) were calculated as $SUVR_{max} = SUV_{max} / SUV^{bm}$ and $SUVR_{iso} = SUV_{iso} / SUV^{bm}$, respectively. Bone marrow SUVs were not evaluated for the patients in the staging study because the software did not include the vertebral column in the 5-compartment attenuation maps of these single-bed-position, pelvic data sets. All SUVs and SUVRs were obtained separately from the PET images reconstructed with the 4 and 5-compartment attenuation maps. For each VOI, the relative change in SUV was calculated as $\Delta SUV = (5\text{-compartment SUV} / 4\text{-compartment SUV} - 1) \times 100\%$, and the relative change in SUVR as $\Delta SUVR = (5\text{-compartment SUVR} / 4\text{-compartment SUVR} - 1) \times 100\%$. In addition, each lesion's distance to the nearest bone was calculated as the shortest Euclidean distance (mm) from the position of SUV_{max} on the PET image reconstructed with the 5-compartment attenuation map to the positions of the bone voxels on the 5-compartment attenuation map.

The 5-compartment attenuation maps were visually compared to the in-phase DIXON MR images and bone registration errors near the lesion VOIs were reported. Since a substantial amount of bone registration errors were found near primary prostate tumors (see results), we specifically evaluated the bias in ΔSUV in these regions; for each patient with bone registration errors near a primary tumor, 2 spherical VOIs of the same size were placed in prostate areas with and without mis-registered bone, respectively. The mean SUV was obtained for both VOIs and ΔSUV s were calculated as described above.

The initial VOIs (before iso-contouring) were delineated using OsiriX (20) (primary tumor VOIs) or ITK-SNAP (21) (all other VOIs). Subsequent iso-contouring, SUV analysis, and calculation of distance to the nearest bone was performed in MATLAB 9.2 (The MathWorks Inc., Natick, MA).

Statistical Analysis

For the lesions without bone registration errors, linear mixed effects models were used to test if ΔSUV and ΔSUVR were different than zero, and to assess if ΔSUV and ΔSUVR were associated with the lesion's distance to the nearest bone. Furthermore, linear mixed effects models were used to test if ΔSUV was different between lesions with and without bone registration errors. In all cases, patient number was used as a random effect on the intercept to account for multiple lesions per patient. The Wilcoxon signed-rank test was used to test if ΔSUV was different between prostate areas with and without mis-registered bone. P-values < 0.05 were considered significant. MATLAB 9.2 was used for statistical analysis.

RESULTS

The imaging data from 28 patients scanned between May 2014 and May 2015 as part of the staging study, and 81 patients scanned between September 2015 and September 2016 as part of the recurrence study, were retrospectively analyzed. Twelve (12) patients from the staging study were excluded for further analysis because of missing PET raw data (N = 10), complete failure of bone inclusion in the 5-compartment attenuation map (N = 1), or artefacts due to a hip prosthesis (N = 1). Fifty-eight (58) patients from the recurrence study were excluded from further analysis because there were no PET findings (N = 58). In the remaining 39 patients (N = 16 staging study, N = 23 recurrence study), a total of 62 lesions was evaluated (n = 28 staging study, n = 34 recurrence study). The median (range) PSA values were 16.7 (3.7 – 56.9) ng/mL and 1.7 (0.2 – 12.3) ng/mL for the patients from the staging and recurrence study, respectively.

Bone registration errors were found near 14/22 (64%) primary tumors (staging study), 1/6 (17%) pelvic lymph node metastases (staging study), 1/8 (13%) locally recurrent tumors (recurrence study), 2/21 (10%) pelvic lymph node metastases (recurrence study), 0/4 (0%) paraaortic lymph node metastases (recurrence study), and 1/1 (100%) bone metastases (recurrence study). Example cases are provided in Figure 1. $\Delta\text{SUV}_{\text{max}}$ and $\Delta\text{SUV}_{\text{iso}}$ were not significantly different between lesions with and without bone registration errors, neither for primary tumors alone (p = 0.299 and 0.282, respectively), nor for all lesions combined (p = 0.125 and 0.241, respectively). The largest increase in SUV was found for the bone lesion ($\Delta\text{SUV}_{\text{max}} = 9.0\%$; $\Delta\text{SUV}_{\text{iso}} =$

8.8%), despite sub-optimal co-registration of the bone atlas (Fig. 1D). In patients with bone registration errors near primary tumors, ΔSUV was significantly higher in prostate regions with than without mis-registered bone ($p < 0.001$). The median (range) bias in prostate regions with bone registration errors was +9.6 (4.4 – 20.2) percentage point.

For the 43 lesions without artefacts, inclusion of bone in the attenuation map was associated with small but significant overall increases in SUV_{max} and SUV_{iso} [$\Delta\text{SUV}_{\text{max}} = 2.5\%$, 95% confidence interval (CI) 2.0%-3.0%, $p < 0.001$; $\text{SUV}_{\text{iso}} = 2.5\%$, 95% CI 1.9%-3.0%, $p < 0.001$]. Figure 2A shows that the effect was similar for the prostate (bed) lesions ($n = 15$; $\Delta\text{SUV}_{\text{max}} = 2.2\%$, 95% CI 1.6%-2.9%, $p < 0.001$; $\Delta\text{SUV}_{\text{iso}} = 2.4\%$, 95% CI 1.4%-3.3%, $p < 0.001$) and the lymph nodes lesions ($n = 28$; $\Delta\text{SUV}_{\text{max}} = 2.6\%$, 95% CI 1.9%-3.3%, $p < 0.001$; $\Delta\text{SUV}_{\text{iso}} = 2.5\%$, 95% CI 1.8%-3.2%, $p < 0.001$). Neither $\Delta\text{SUV}_{\text{max}}$ ($p = 0.964$) nor $\Delta\text{SUV}_{\text{iso}}$ ($p = 0.620$) was associated with the lesion's distance to the nearest bone (Fig. 3A).

The inclusion of bone in the attenuation map was not associated with significant changes in SUVR_{max} or SUVR_{iso} when all lesions of the recurrence study were considered ($\Delta\text{SUVR}_{\text{max}} = 0.2\%$, 95% CI -0.5%-0.9%, $p = 0.604$; $\Delta\text{SUVR}_{\text{iso}} = 0.2\%$, 95% CI -0.6%-1.0%, $p = 0.581$). Again, the results were comparable between prostate (bed) lesions ($\Delta\text{SUVR}_{\text{max}} = 0.4\%$, 95% CI -1.4%-2.1%, $p = 0.676$; $\Delta\text{SUVR}_{\text{iso}} = 0.8\%$, 95% CI -1.8%-3.3%, $p = 0.562$) and lymph node lesions ($\Delta\text{SUVR}_{\text{max}} = 0.1\%$, 95% CI -0.7%-1.0%, $p = 0.737$; $\Delta\text{SUVR}_{\text{iso}} = 0.1\%$, 95% CI -0.7%-0.9%, $p = 0.581$) (Fig. 2B) and no significant associations

were found between with $\Delta\text{SUVR}_{\text{max}}$ ($p = 0.982$) or $\Delta\text{SUVR}_{\text{iso}}$ ($p = 0.797$) and distance to bone (Fig. 3B).

DISCUSSION

Promising results from several studies with different radiopharmaceuticals indicate that PET/MRI has the potential to play an important role in staging of primary prostate cancer, e.g. (4,18,22,23), and detection of disease recurrence after initial treatment with curative intent, e.g. (24-27). However, in current clinical practice, the high linear attenuation coefficients of the bones in the pelvis and lower abdomen are assumed to be equal to those of soft tissue, which is incorrect. In this study, we applied a commercially available atlas-based method for including bone in the attenuation maps and evaluated its effect on the SUVs and SUVRs of primary and recurrent prostate cancer lesions. We found that including bone resulted in significant but small increases in the SUV of prostate (bed) and lymph node lesions, which were in the order of 2 to 3%. These results agree well previously reported observed and simulated bias values from ignoring bone attenuation (11,13-15). We did not observe an effect of including bone attenuation on lesion-to-bone marrow SUVRs, as the increases in SUV were similar for the lesion and bone marrow. Based on these results, and the bone registration errors discussed below, we deem the inclusion of bone in the PET/MRI attenuation maps not recommendable for the evaluation of soft tissue prostate cancer lesions.

We found that bone registration errors may pose a problem in some patients, especially for prostate (bed) lesions when scanned in a single bed position. For the lesions analyzed in this study, the effect of including bone was not significantly different

between lesions with and without bone registration errors. However, we did observe a significant bias in Δ SUV of approximately +10 percentage points when comparing prostate areas of the same patient with and without mis-registered bone. These local inaccuracies could potentially misguide clinical decision making and need to be resolved before we would advise this method for routine clinical prostate cancer imaging. Recently, acceleration techniques have been proposed which enable acquisition of higher-resolution DIXON images in the same scan time (28). In a study with 51 patients who underwent whole-body ^{18}F -FDG PET/MRI with high-resolution DIXON imaging, Oehmigen *et al* did not observe any bone registration errors in the 5-compartment attenuation correction maps (15), which indicates that the higher level of anatomical detail in these images might lead to better results. High-resolution DIXON imaging was yet not available on our scanner when the data of this study were acquired; however, a direct comparison of pelvic bone registration errors in 5-compartment attenuation maps obtained from standard and high-resolution DIXON images is subject of future research.

A limitation of this study is that only one bone lesion was present in the evaluated patient cohort. Moreover, the lesion-containing bone was not correctly registered when included in the 5-compartment attenuation map, which hampered proper comparison of SUVs between attenuation methods. Nevertheless, the relatively large increase in SUV observed for the bone lesion points towards a substantial effect of the attenuation correction method for this lesion type. Similar differences in bone

lesion SUV between PET images reconstructed with the 4 and 5-compartment attenuation maps were found by others (14,15). Consequently, it would be recommendable to perform an additional reconstruction with a 5-compartment attenuation map when bone lesions are suspected based on the PET images reconstructed with the 4-compartment attenuation map.

Another limitation of this study is the lack of CT-based attenuation correction maps as a gold standard. Both the staging study and the recurrence study were PET/MRI only, so CT-derived attenuation maps of the same patients were not available for comparison. However, direct comparison between MRI and CT-derived attenuation correction is also challenging, as it is virtually impossible to keep the patient in the exact same position when scanned in a different scanner at a different time point. Our results are valuable because they show that atlas-based inclusion of bone in the attenuation maps is not likely to affect the clinical evaluation of soft tissue lesions on ¹⁸F-fluciclovine PET/MR images of primary and recurrent prostate cancer, in spite of the high bone density of the pelvis. These results are in accordance with Oehmigen et al, who show that truncation of the arms is a larger source of SUV bias in the pelvis than ignoring bone (15). Whether our results are also valid for prostate cancer imaging with other PET radiopharmaceuticals, including prostate specific membrane antigen (PSMA) and choline-based tracers, remains to be seen and will be part of future research. In all cases, the atlas-based method may be important for the quantification of uptake in

bone lesions, but the attenuation maps should always be checked for bone registration errors.

CONCLUSION

The investigated method for atlas-based inclusion of bone in DIXON-based attenuation correction of ^{18}F -fluciclovine PET/MRI has only a small effect on the SUVs of soft-tissue prostate cancer lesions, and no effect on their lesion-to-bone marrow SUVRs when using signal from L3 as a reference. The attenuation maps should always be checked for bone registration errors when evaluating lesions in or close to the bones.

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FIGURES

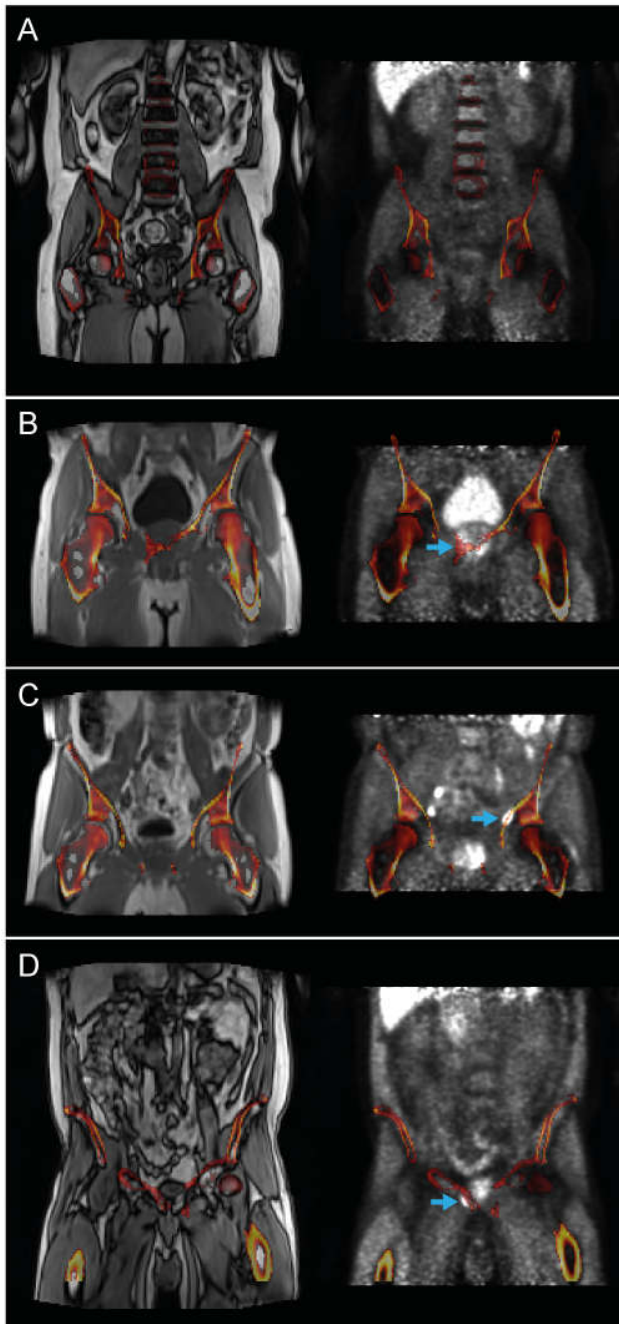


Figure 1. Coronal in-phase DIXON MR (left) and PET images reconstructed with the 4-compartment attenuation map (right) images overlaid with the 5-compartment attenuation map (linear attenuation coefficient $> 0.1 \text{ cm}^{-1}$, i.e. bone only) for a case without bone registration errors (A) and cases with bone registration errors near a primary tumor (B), pelvic lymph node metastasis (C), and bone lesion (D), as indicated by the blue arrows

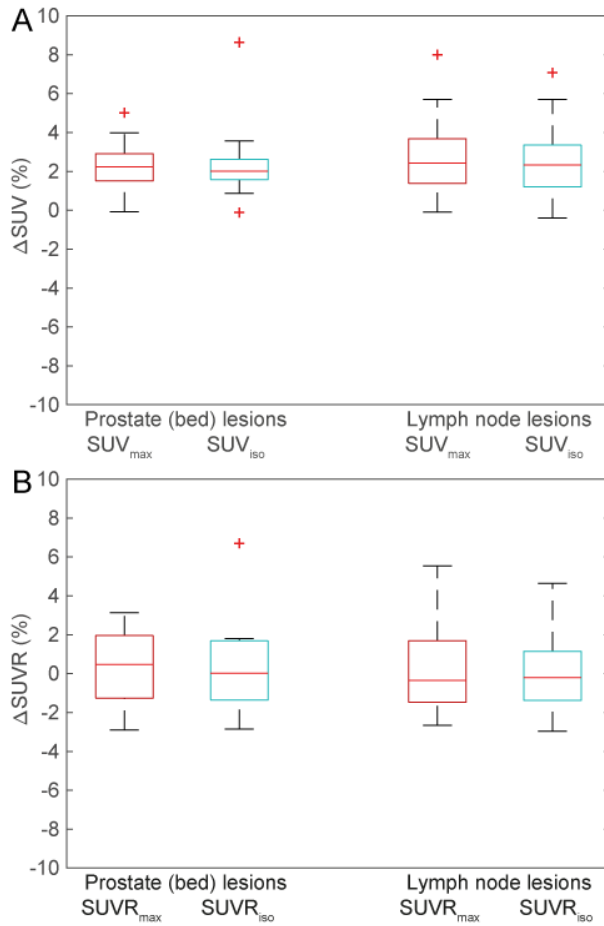


Figure 2. Box plots of the relative difference in SUV (ΔSUV , A) and lesion-to-bone marrow SUV ratio (ΔSUVR , B) between PET images reconstructed with the 4 and 5-compartment attenuation maps. Including bone in the attenuation map was associated with significant increases in maximum and mean SUV (SUV_{max} and SUV_{iso} , respectively) for both prostate (bed) and lymph node lesions. However, no significant changes were observed in maximum and mean SUVR (SUVR_{max} and SUVR_{iso} , respectively)

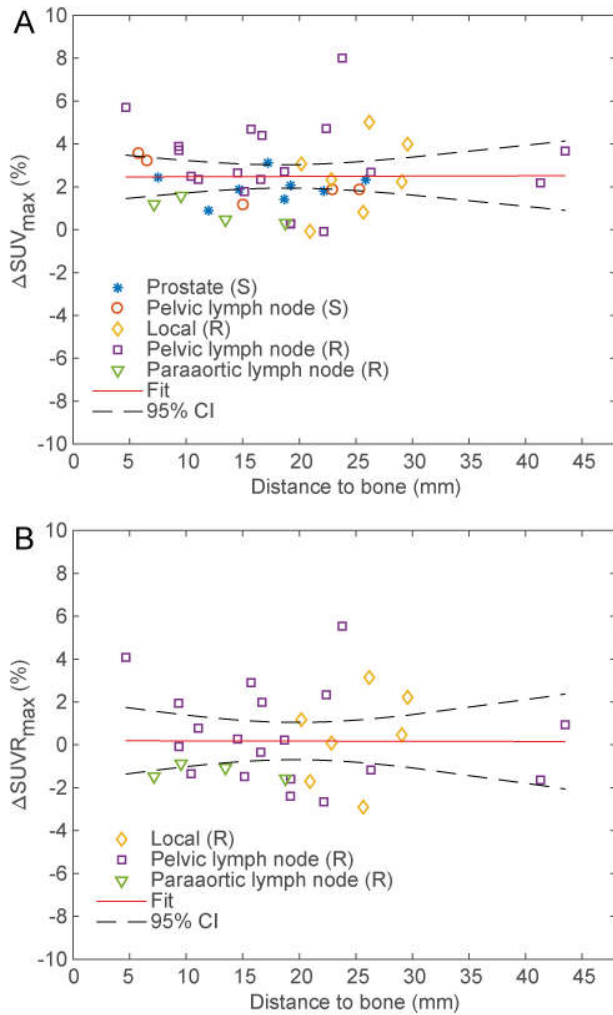


Figure 3. Plot showing the relative difference in maximum SUV ($\Delta\text{SUV}_{\text{max}}$, A) and maximum lesion-to-bone marrow SUV ratio ($\Delta\text{SUVR}_{\text{max}}$, B) between PET images reconstructed with the 4 and 5-compartment attenuation maps, plotted as a function of distance to the nearest bone. Linear mixed effect models analysis revealed that there were no significant associations between $\Delta\text{SUV}_{\text{max}}$ or $\Delta\text{SUVR}_{\text{max}}$ and the distance to

bone, as also illustrated by the horizontal lines of the model fits. (S) = staging study; (R)
= recurrence study; CI = confidence interval