Phantom and clinical evaluation of bone SPECT/CT image reconstruction with xSPECT algorithm

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Abstract

Background Two novel methods of image reconstruction, xSPECT Quant (xQ) and xSPECT Bone (xB) that use an ordered subset conjugate gradient minimizer (OSCGM) for bone SPECT/CT have been proposed. The present study compares the performance characteristics of xQ, xB and conventional Flash3D (F3D) reconstruction using images derived from phantoms and patients.

Methods A custom-designed body phantom for bone SPECT was scanned using a Symbia Intevo (Siemens Healthineers) and reconstructed xSPECT images were evaluated. The phantom experiments proceeded twice in different activity concentrations and sphere sizes. A phantom with 28-mm spheres containing a 99mTc background and having tumor-to-normal bone ratios (TBR) of 1, 2, 4 and 10, were generated and its convergence property was evaluated across 96 iterations. A phantom with four spheres (13-, 17-, 22-, and 28-mm diameters), containing a 99mTc-background at TBR4, was also generated. The full width at half maximum of an imaged spinous process (10 mm), coefficients of variance (CV), contrast-to-noise ratio (CNR) and recovery coefficients (RC) of an imaged spine were evaluated with F3D, xQ and xB. Images from 20 patients with suspected bone metastases (male, n = 13) were acquired using 99mTc-(H)MDP SPECT/CT, then the CV and standardized uptake value (SUV) at the 4th vertebral body (L4) were compared with xQ and xB in a clinical setup.

Results Mean activity concentrations with various TBR converged accordance to increasing numbers of iterations. Spatial resolution was improved in the order of xB, xQ and F3D regardless of the number of iterations during reconstruction. The CV and RC were better for xQ and xB than for F3D. The CNR peaked at 24 iterations for xQ and 48 iterations for F3D and xB, respectively. The RC significantly differed between xQ and xB at lower numbers of iterations, whereas those of xQ and xB became almost equivalent at higher numbers of iterations. Significant differences in the clinical patients’ SUVmax and SUVpeak were observed in the reconstructed xQ and xB images.

Conclusions The reconstructed xQ and xB images were more accurate than those conventionally reconstructed using F3D. Bone SPECT xB imaging offered essentially unchanged spatial resolution even when the numbers of iterations did not converge. The xB further enhanced SPECT image quality using CT data. Our findings provide important evidence for understanding the performance
characteristics of the novel xQ and xB algorithms.

Background

Traditional bone imaging using $^{99m}$Tc-labeled phosphate compounds are widely applied as diagnostic tools for detecting osseous metastases and staging malignant disease [1-3]. Hybrid imaging using single-photon emission computed tomography/computed tomography (SPECT/CT) for bone imaging can enhance image quality due to attenuation correction (AC) and scatter correction (SC) and tracer uptake is precisely localized. Römer et al. showed that 92% of indeterminate lesions could be correctly classified by SPECT/CT with a pronounced benefit for bone lesions [4]. Utsunomiya et al. also reported significantly improved diagnostic confidence for fused SPECT/CT image datasets compared with side-by-side views of images from both modalities [5]. Hybrid SPECT/CT imaging in three dimensions (3D) has overcome the problem of planar bone imaging, which has high sensitivity but low specificity and thus improves the accuracy of diagnosing bone lesions [6, 7].

Recent advances in SPECT technology have included not only hardware but also software, such as image reconstruction. Absolute quantitation of $^{99m}$Tc bone SPECT/CT has become important as a diagnostic tool and as a means of monitoring treatment effects [8,9]. Previous phantom and clinical studies have found that the quantitative accuracy of SPECT imaging using $^{99m}$Tc is within ±10% [10, 11]. A multicenter study of four SPECT/CT systems also maintained quantitative accuracy within 10% using 3D iterative reconstruction with AC, SC and resolution recovery [12]. However, further reliable quantitative data accumulation is needed for the common use of quantitative bone SPECT imaging in clinical diagnosis. Currently, the need and importance of developing novel SPECT imaging techniques associated with absolute SPECT quantitation have been discussed in terms of such as cost, standardized uptake values (SUV) and dosimetry [13-15]. The quantitative SPECT/CT complements the poor aspects of positron emission tomography and has contributed to the rapid development of quantitative nuclear medicine applications [16,17].

Improved spatial resolution of SPECT images helps in quantitative improvement as well as in the detection and precise localization of small lesions [18]. However, the spatial resolution of SPECT images still remains poor. Tsui et al. suggested that multimodal image reconstruction would
remarkably improve SPECT image quality [19]. Kuwert et al. also focused on quantitation and the above reconstruction technique as a methodological advance to further improve the value of bone SPECT/CT imaging [13]. The impact of SPECT imaging using this multimodal reconstruction should be verified, but SPECT imaging using this novel reconstruction methodology should be more quantifiable and have with excellent diagnostic confidence.

Siemens® has introduced a technology called “xSPECT”, which includes a novel iterative image reconstruction algorithm (ordered subset conjugate gradient minimizer; OSCGM) based on the conventional ordered subset expectation maximization (OSEM; Flash 3D; F3D) to improve multimodal alignment in image space, and thus enhance image quality. Onoguchi et al. described the differences between OSEM and OSCGM algorithms in detail [20]. Briefly, the xSPECT technology applies the Mighell merit function to suppress the noise caused by the fast convergence of OSCGM reconstruction. Additionally, the use of a National Institute of Standards and Technology (NIST) traceable calibration $^{57}$Co point source with a 3% uncertainty (99% confidence level) was introduced by Siemens® to low-energy radionuclides for $^{99m}$Tc to enable standardization of quantitative SPECT. The SPECT voxel counts based on accurate correction can convert to activity concentration (Bq/mL) with a system planar sensitivity correction factor measured with this point source during reconstruction. This method of quantitative reconstruction is called “xSPECT Quant” (xQ). Siemens® also concurrently released bone-specific software with xSPECT features called “xSPECT Bone (xB)” [21], in which higher-resolution CT data were added to enhance reconstructed images at tissue boundaries. Therefore, xB produces images of tracer distribution with far better quality than F3D [22]. Some clinical reports have described that xB images for bone SPECT are more precise in terms of localization and offer better diagnostic confidence in staging malignant disease [23-25].

The fundamental theory of xB is that the use of image space minimizes interpolation errors in information obtained from anatomical modalities, and reconstructed images have high spatial recognition due to denser spatial sampling. However, the xQ applies a CT-derived reconstruction mask to reduce background noise [26]. When comparing the two reconstruction methods, researchers
found an unexpected behavior in xQ, where the subset >2 decreased image quality [27, 28]. For both xQ and xB, developers also found that the 3-degree sampled data have lower noise and higher resolution than those for 6-degree sampling [29]. Typically, quantitative and physical indexes such as recovery coefficients (RC), SUV and noise characteristics depend on the SPECT image reconstruction and the reconstruction parameters. Although xSPECT imaging also similarly depends on different reconstruction parameters, the impact of qualitative and quantitative xSPECT imaging has not yet been clarified. The present study aimed to determine the performance characteristics of the novel xSPECT algorithm. To our knowledge, this is the first attempt to clarify the functional differences between xQ and xB based on phantom measurements and clinical data.

Methods

Data acquisition and reconstruction

All imaging data were acquired using a Symbia Intevo16 hybrid SPECT/CT system (Siemens Healthineers, Erlangen, Germany) comprising an integrated dual-head SPECT camera with a 16-slice helical CT scanner. We acquired SPECT images under the following parameters: ±7.5% energy window at 140 keV with a lower scatter window of 15%, ⅜” crystal thickness, low-energy high-resolution collimator, 256 × 256 matrix with 2.4-mm pixels and a total of 120 projections of 15 s/view over 360° in a non-circular orbit continuous acquisition mode. Immediately following the SPECT acquisition, CT images were acquired at 130 KV and 70 ref mA using adaptive dose modulation (CARE Dose 4D; Siemens Healthineers) with a 512 × 512 matrix, pitch 1.5, 0.8-s rotation and 2 × 1.5-mm collimation. The CT data were reconstructed at a 3.0-mm slice thickness using a B31s attenuation filter (Siemens Healthineers).

We reconstructed the SPECT images using the algorithms F3D, xQ and xB and a 6-mm 3D Gaussian filter with various combinations of one fixed subset and 1-96 iterations. The F3D is equipped with OSEM and depth-dependent 3D resolution recovery using the Gaussian point-spread functions, AC and SC. The xQ and xB are equipped with OSCGM and depth-dependent 3D resolution recovery using AC and SC. The xB algorithm divides CT pixels into six tissue classes with smooth boundaries based on CT values or “zones” of air and lung, adipose, soft tissue, soft bone, cortical bone, metal material, and
updates. The xB iterative operation can be weighted according to the corresponding zone class in the divided pixel, however, the iterative operation for each zone class based on the CT data showed no effect in raising the original count [24].

**Cross-calibration of SPECT imaging**

Reconstructed SPECT counts derived from F3D and xSPECT were converted to activity concentrations based on a cross-calibration factor (CCF) obtained from the relationship between the reconstructed counts and activity concentrations and system planar sensitivity, respectively, for quantitative comparisons. In SPECT images using F3D, a circular region of interest (ROI) to measure SPECT count density (counts/mL) was placed at the center of the cylindrical phantom on the central slice and at ±1 and ±2 slices from the center. The CCF was automatically calculated using GI-BONE software (Aze, Tokyo, Japan) software as the ratio of the actual activity concentration (measured by the dose calibrator) in the phantom at the time of scanning to the measured SPECT counts density per scan duration [30].

The using dose calibrator used for cross-calibration was CRC-15R (final calibration date by manufacturer: 4/19/2005). The dose calibrator is also confirmed and calibrated with a cite-specific NIST traceable $^{68}$Ge/$^{68}$Ga source every 3 months (final calibration date in site: 12/18/2019) [31, 32]. Therefore, we consider that the uncertainty of the measurement by the dose calibrator is small. The actual SUV was calculated as:

Reconstruction with xQ and xB precisely determine images in units of Bq/mL that are converted using system planar sensitivity with NIST traceable $^{57}$Co source [21]. The system planar sensitivity is a necessary parameter to allow for the conversion between the count rate and units of absolute activity. This is defined as a measure of how many counts the gamma camera detects for every unit of activity in its field of view. Therefore, system planar sensitivity was measured with traceable point source without scattering and attenuation to realize accurate and reproducible quantitation [28, 33].

The use of this source is recommended for all Siemens® users to improve SPECT quantification. We
automatically converted the quantitative SPECT/CT data using MI Applications VB10 (Siemens Healthineers).

**Phantom Studies**

*Phantom design*

We custom-designed a physical three-dimensional phantom to determine the bone SPECT-specific distribution of activity and the linear attenuation coefficient (Figure 1). This phantom can be used to generate SPECT images of bone metastasis with a realistic abdomen contour [34]. The phantom contains a $^{99m}$Tc solution to simulate the soft tissue, and the vertebral body, spinous and transverse process and tumor region contained a bone-equivalent solution of $K_2HPO_4$ and $^{99m}$Tc [35]. The phantom experiments proceeded twice using different activity concentrations and sphere sizes as follows. Tumor, normal bone and soft tissue in the phantom are filled with $^{99m}$Tc solution. In the first round of experiments, a body phantom with four 28-mm diameter spheres was set and acquired at tumor-to-normal bone ratios (TBR) of 1, 2, 4 and 10 at a normal bone activity level of 50 kBq/mL. This phantom contained 8 kBq/mL of a $^{99m}$Tc solution as the background activity of the soft tissue. That is, in the case of TBR1, there is no difference between the boundary and the background, and the difference in the activity concentration increases as a function of the higher TBR. In the second round of experiments, another phantom was set as 13-, 17-, 22-, 28-mm diameter spheres and used to determine the activity concentrations of the simulated soft tissue, normal bone and tumor at 8, 50 and 200 kBq/mL, respectively, i.e., TBR4.

**Figure 1**

*Data Analysis*

The SPECT acquisition data in the first round of experiments were reconstructed using subset 1 and 1-96 iterations. We examined the effects of the reconstruction algorithms on various TBR in the 28-mm
sphere and then determined the optimal reconstruction parameters in accordance with the result of this convergence characteristic. Phantom images containing different sizes of simulated tumors were continuously analyzed in terms of the spatial resolution of a 10-mm spinous process, the coefficient of variance (CV) and the contrast-to-noise ratio (CNR) of the vertebral body and RC as quantitative parameters. We drew profile curves on the spinous process, measured the full width at half maximum (FWHM), and evaluated the CV at an 80% circular ROI (ROI80%) placed at the center of the vertebral body. The RC were placed at circular ROI with diameters of 13, 17, 22, 28 mm. The CV was calculated as SD/mean, where SD represents the standard deviation of the ROI in the radioactive section and mean represents the mean SPECT value (kBq/mL) in the ROI. The CNR at TBR 4 was calculated as (Hs-Hnb) / σnb, where, Hs and Hnb are the activity concentrations measured in the spheres and normal bone, respectively, and σnb is the voxel SD in the normal bone. The RC was defined as the ratio of the mean SPECT value (kBq/mL) and the true SPECT value (kBq/mL) for each sphere.

Clinical study

Imaging protocol

We analyzed data from 20 consecutive patients who had undergone bone SPECT/CT imaging for metastatic prostate or breast cancer (male, n = 13; female, n = 7; median age, 62 years; range, 40–83 years; average weight, 65.2 ± 13.4 kg; range, 51.8–78.6 kg). The optimal condition of the convergence characteristic in the phantom study was applied in the clinical reconstruction parameters in xQ and xB. Bone SPECT/CT imaging proceeded from the abdomen to the pelvis ~2.5–4 h after delivering an intravenous injection of 1003.4 ± 102.8 MBq $^{99m}$Tc-methylene diphosphonate ($^{99m}$Tc-MDP; FUJIFILM Toyama Chemical, Tokyo, Japan) or hydroxymethylene diphosphonate ($^{99m}$Tc-HMDP; Nihon Medi-Physics, Tokyo, Japan). The average amount of injected $^{99m}$Tc was 15.9 ± 2.8 (range, 13.1–18.7) MBq/kg. The Ethics Committee at the Cancer Institute Hospital of JFCR approved this clinical study (approval no. 2015-1151). These clinical data were analyzed in this retrospective study and the results did not influence any further therapeutic decision-making.
Data analysis

The noise characteristics and quantitative performance of the clinical SPECT image were analyzed at the level of the 4th vertebral body (L4) [36]. We placed a ROI80% on the center of the axial slice in the vertebral body section, and a ROI80% exactly on the corresponding vertebral body in the central slice by following the CT boundaries of the fused SPECT/CT images (Figure 2). We determined as the SUV$_{\text{max}}$, SUV$_{\text{mean}}$ and SUV$_{\text{peak}}$ as normalized by the patient’s body weight. These data were analyzed using PETSTAT software (AdIn Research, Tokyo, Japan).

Figure 2

Statistical analysis

All SUV and CV indices in the xQ and xB groups were compared using Wilcoxon signed-ranks tests after evaluating the non-normal distribution using Kolmogorov-Smirnov tests. Values were considered statistically significant when $P < 0.05$. These data were statistically analyzed using SPSS Statistics software (IBM, Armonk, NY, USA).

Results

Phantom studies

Convergence for various TBR

Figure 3 shows the SPECT data reconstructed using between 1 and 96 iterations. Regardless of the reconstruction model and iteration number, the mean activity concentrations gave better results than did the maximum activity concentrations for the two lowest TBR values (Fig. 3A, 3B) whereas maximum activity concentrations gave better results for the highest TBR values (Fig. 3C, 3D). In addition, the maximum activity concentrations with F3D showed the highest values, which were better than for both xQ and xB at TBR 10 (Fig. 3D). On the other hand, the maximum activity concentration with xSPECT did not converge and increased in proportion to the number of iterations. The mean activity concentration converged with increasing iterations regardless of the TBR. The mean activity concentrations of xQ and xB were essentially equivalent at $>24$ iterations. The mean activity concentration was lower for F3D than xQ and xB.
**Spatial resolution**

Figure 4 shows the spatial resolution of the spinous process for various iterations. The FWHM with xQ and F3D improved considerably when the iteration number increased, but the spatial resolution produced by the xB algorithm was the best. The FWHM of the xQ and F3D reconstructions converged at about 15 and 20 mm, respectively. In contrast, the xB values remained similar to the actual size (10 mm) regardless of iterations. Figure 5 shows the results of the SPECT images with 48 iterations according to each reconstruction model. The reconstructed F3D and xQ bone SPECT images of the boundaries of the vertebral body were visually indistinct, whereas the boundary between normal bone and the hot sphere was clearly visible in the reconstructed xB images. Both xB and F3D produced visually clearer images than did xQ in terms of background noise.

**Noise characteristics**

Figure 6 and Figure 7 show the CV and CNR of the vertebral body according to the number of iterations, respectively. Although the CV increased in the order of xB, xQ and F3D as the number of iterations increased, the amount of noise was similar between xQ and xB. The CV of xQ and xB at >24 iterations were both relatively stable at 0.2. The mean and max CNR showed similar results for each reconstruction. Although the mean CNR is better in the order of xB, xQ and F3D as the number of iterations increased, the CNR of F3D and xB at > 48 iterations, xQ at > 24 iterations decreased, respectively.

**Recovery coefficient**

Figure 8 shows the RC of the vertebral body for 12–96 iterations. The RC in all algorithms improved with increasing sphere size. The RC was relatively higher with xB, than the other algorithms at 12 iterations; the differences in the RC between xQ and xB were essentially equivalent as a function of the increasing numbers of iterations. The RC was lower for F3D than xQ and xB at the
same number of iterations, but the RC of F3D after iteration 36 was better than that of xQ after iteration 12 (Fig. 8G).

Figure 8

Clinical study

Table 1 shows the $\text{SUV}_{\text{max}}$, $\text{SUV}_{\text{peak}}$, $\text{SUV}_{\text{mean}}$ and CV under clinical conditions. The quantitative SPECT values for some patients showed much higher values than those of the others. The statistical findings showed a significant difference in the $\text{SUV}_{\text{max}}$ and $\text{SUV}_{\text{peak}}$ between xQ and xB. However, $\text{SUV}_{\text{mean}}$ and CV on SPECT images reconstructed with xQ and xB did not significantly differ ($P > 0.05$).

Table 1. The $\text{SUV}_{\text{mean}}$, $\text{SUV}_{\text{max}}$, $\text{SUV}_{\text{peak}}$ and CV of the 4th vertebral body in xQ and xB

[Please see the supplementary files section to view the table.]

Discussion

We validated novel xSPECT and conventional F3D reconstruction using the experimental data derived from phantoms. Additionally, using the clinical data derived from patients was evaluated the quantitative difference between xB and xQ. The phantom experimental findings indicated that the image quality and quantitative accuracy of xSPECT considerably exceeded those of F3D. However, the xQ without weighted correction had obviously a visual difference in the background noise than for F3D due to the increasing noise caused by fast convergence. We also found that xB can maintain high spatial resolution even at various numbers of iterations. The $\text{SUV}_{\text{max}}$ and the $\text{SUV}_{\text{peak}}$ in our clinical study showed significant differences between xQ and xB; thus, we concluded the xB has an essential particular to the diagnostic tools for bone SPECT images in terms of its high quantitation and spatial resolution.

Regardless of the reconstruction models, the maximum activity concentration on the spheres in TBR1 and TBR2 was overestimated compared to actual activity concentration (Fig. 3). This considers that the maximum activity concentration on the sphere became theoretically higher because of the increasing statistical noise at the lower count. Akamatsu et al. also showed $\text{SUV}_{\text{max}}$ resulted in
overestimation as the image noise increased [35]. In a unique point from Figure 3D, the results of F3D at the maximum activity concentration exceeded that of xSPECT. The merit function incorporated in xSPECT may enhance the noise suppression as a function of higher activity concentration. However, xSPECT reconstruction has many unknown behaviors; therefore, this potentially represents only one potential explanation. In contrast, the mean activity concentration approached the actual activity concentration in accordance with the lower TBR. When the tumor and normal bone were equal (TBR = 1), there is not spill-out by partial volume because the activity concentrations inside and outside the ROI were almost equivalent. TBR 1 was slightly overestimated due to the activity concentration being increased by the statistical noise. At the higher TBR, the mean activity concentration underestimated as a result of spillage from the sphere to the background [36]. The quantitative differences between F3D and xSPECT are influenced both statistical noise based on convergence and partial volume effect caused by lower spatial resolution. Our results showed that the mean activity concentrations essentially converged within 48 iterations, but the mean activity concentrations for xQ and xB were similar converged similarly at >24 iterations. The FWHM for the xQ after 36 iterations converged and showed results almost equivalent to the RC of the xB. The number of iterations recommended for Siemens® SPECT is 48 iterations [28], but the maximum activity concentrations with xSPECT did not converge at high numbers of iterations. The number of iterations is associated with a trade-off between signal and noise. Considering the increase in noise, we determined that 30 iterations were the most appropriate for xSPECT reconstruction in clinical practice. The FWHM of F3D after >40 iterations compared to xQ at 12 iterations was higher because of the faster convergence; however, the FWHM with xQ and F3D considerably improved and fully converged at ~15 and 20 mm, respectively, when the high number of iterations. Therefore, image quality for xQ was better than F3D at the appropriate parameter. In contrast, the xB algorithm with divided into zone classes shows unique results unlike the observed xQ. The spatial resolution for xB almost unchanged even when the number of iterations increased, and the actual size of 10 mm was almost achieved. The zone class of each tissue is derived from based on the high-resolution CT showing delineated edges; therefore, the FWHM of xB determines related to CT resolution. Additionally, the xB
iterative operation is weighted by zero or any other value according to the corresponding zone class in the divided pixel [21]. We considered that not only bone classes weighted by the optimal value, but also non-bone classes weighted by zero with a zonal map were responsible for the improved spatial resolution using the xB technology.

The xSPECT enhances SPECT images by applying the merit function to suppress noise caused by the fast convergence of OSCGM reconstruction. This reconstruction using the merit function adopts the Mighell-modified chi-squared gamma statistic algorithm. Shinohara et al. indicated that Mighell-modified noise suppression was better than other image reconstructions based on chi-square statistics [39]. The CV of xQ and xB did not exceed that of F3D of 12 iteration numbers regardless of the number of iterations. Thus, the xSPECT with the Mighell-modified merit function considerably suppressed the noise compared with F3D algorithms under the same number of iterations. For the one subset of reconstructed images, a more apparent problem is the increasing image noise in the background region and hot sphere according to the number of iterations. On the other hands, the background noise in the xQ increased rapidly and appeared to differ from other reconstructed images at 48 iterations (Fig. 5). However, Armstrong et al. have reported the greatest CNR in xQ is achieved with 48 iterations for one subset [27]. Our results indicated the greatest CNR for xQ at 24 iterations and a higher RC than for F3D at 48 iterations (Fig. 7, Fig. 8). On the other hand, the xB suppressed image noise more effectively than F3D and xQ. The xB reconstruction has the weighted correction every zone classes, and the impact of noise suppression differed between xQ and xB [40]. The CNR in xB showed greatest at iteration 48, noise suppression was decreased in xB > 48 iterations. In regions with inadequate uptake such as the soft tissue, not only the xQ based on the OSCGM algorithm might lead to the increasing CV by iteration setting but also have ramifications for lesion detectability. Therefore, the xQ should be further required careful optimization of iteration numbers than F3D and xB.

The present study examined 20 patients with suspected bone metastases. The SPECT values of measured L4 had a wide SUV range because of the patients including various diseases (bone metastasis 7 patients, degenerative 5 patients, trauma 3 patients and normal 5 patients,
respectively). Our clinical study showed a significant difference in $SUV_{\text{peak}}$ $SUV_{\text{max}}$, and this quantitative difference between xQ and xB could interpret as noise suppression caused by faster convergence. Because the $SUV_{\text{peak}}$ is less susceptible to statistical noise compared to $SUV_{\text{max}}$ [37], $SUV_{\text{peak}}$ showed a more significant difference ($p = 0.001$). The clinical xB image with high resolution reveals not only shows bone microlesions but also improves diagnostic confidence [23]. Therefore, we considered that clinical evaluation for xB images with $SUV_{\text{peak}}$ could provide more accurate and reliable diagnostics. To calculate $SUV_{\text{peak}}$ entails expressing the maximum average voxel value within a 1 cm$^3$ spherical volume, but the xB is useful tools to enhance diagnostics for bone SPECT images in terms of its quantitative and qualitative improvement. However, the quantitative variation caused by misalignments such as motion and respiratory error during clinical scanning is a concern. The xB imaging might cause different behavior due to the unique zone map system. Therefore, the misalignment between SPECT and CT due to respiratory errors such as caused by the ribs and sternum should be considered when clinically applying xB.

The present study has several limitations. The reconstructed SPECT images were assessed using different cross-calibration methods. The CCF on quantitative SPECT images varied depending on the activity concentration [41]. Thus, slight quantitative errors might arise between the F3D and xSPECT models. In addition, the body types of the 20 patients were essentially standard (average, 15.9 ± 2.8 MBq/kg). We could not consider dependence on physique into consideration, and the impact of factors such as counts and scattering remains unclear. Further study is required to assess the relationship between body weight and the quality of images reconstructed using the xSPECT algorithm.

Conclusions
Bone images were qualitatively and quantitatively improved when reconstructed using the OSCGM-based xSPECT (xQ and xB) compared with the OSEM-based F3D reconstruction. The xB images using optimized reconstruction conditions were more sharply demarcated, with better quality, and lower background noise. One unique aspect of the bone structures in xB reconstructions is that the imaged content such as spatial resolution was independent of the number of iterations. Our findings provide
important information that should facilitate understanding of the performance characteristics of the novel xQ and xB algorithms.

Abbreviations

xQ xSPECT Quant
xB xSPECT Bone
OSCGM Ordered subset conjugate gradient minimizer
F3D Flash 3D
FWHM Full width at half maximum
CV Coefficients of variance
RC Recovery coefficients
SUV Standardized uptake value
L4 4th vertebral body
AC Attenuation correction
SC Scatter correction
SPECT/CT Single-photon emission computed tomography/computed tomography
OSEM Ordered subset expectation maximization
CCF Cross-calibration factor
TBR Tumor-to-normal bone ratios
ROI Regions of interest

Declarations

Ethics approval and consent to participate

The Ethics Committee at the Cancer Institute Hospital of JFCR approved this clinical study (approval no. 2015-1151). The results of this retrospective study did not influence any further therapeutic decision-making.

Consent for publication

Not applicable

Availability of data and material
All data generated or analyzed during this study are included in this published article

**Competing interests**

The authors declare that they have no competing interests

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None

**Authors' contributions**

NM contributed to the study design, phantom data acquisition and analysis of the data. KM and MO contributed to the study design, analysis of the data, and draft and critical revision of the manuscript. HI and AT contributed to the preparation of the study and critical revision of the manuscript. HI contributed to phantom data acquisition and interpretation. TT and MK contributed to the critical revision of the manuscript. All authors read and approved of the final manuscript.

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**References**

1. Krasnow AZ, Hellman RS, Timins ME, Collier BD, Anderson T, Isitman AT. Diagnostic bone scanning in oncology. Semin Nucl Med. 1997;27(2):107-141.

2. Hamaoka T, Madewell JE, Podoloff DA, Hortobagyi GN, Ueno NT. Bone imaging in
3. Shen G, Deng H, Hu S, et al. Comparison of choline-PET/CT, MRI, SPECT, and bone scintigraphy in the diagnosis of bone metastases in patients with prostate cancer: a meta-analysis. Skeletal Radiol. 2014;43(11):1503-1513.

4. Römer W, Nömayr A, Uder M, Bautz W, Kuwert T. SPECT-guided CT for evaluating foci of increased bone metabolism classified as indeterminate on SPECT in cancer patients. J Nucl Med. 2006;47(7):1102-1106.

5. Utsunomiya D, Shiraishi S, Imuta M, Tomiguchi S, Kawanaka K, Morishita S, et al. Added value of SPECT/CT fusion in assessing suspected bone metastasis: comparison with scintigraphy alone and nonfused scintigraphy and CT. Radiology. 2006;238:264-271.

6. Even-Sapir E. Imaging of Malignant Bone Involvement by Morphologic, Scintigraphic, and Hybrid Modalities. J Nucl Med. 2005;46(8):1356-1367.

7. Damle NA, Bal C, Bandopadhyaya GP, Kumar L, Kumar L, Kumar P, Malhotra A, et al. The role of 18F-fluoride PET-CT in the detection of bone metastases in patients with breast, lung and prostate carcinoma: a comparison with FDG PET/CT and 99mTc-MDP bone scan. Jpn J Radiol. 2013;31(4):262-269.

8. Cachovan M, Vija AH, Hornegger J, Kuwert T. Quantification of 99mTc-DPD concentration in the lumbar spine with SPECT/CT. EJNMMI Res. 2013;3(1):45.

9. Beck M, Sanders JC, Ritt P, Reinfelder J, Kuwert T. Longitudinal analysis of bone metabolism using SPECT/CT and 99mTc-diphosphonopropanedicarboxylic acid: comparison of visual and quantitative analysis. EJNMMI Res. 2016;6(1):60.

10. Ritt P, Vija AH, Hornegger J, Kuwert T. Absolute quantification in SPECT. Eur J Nucl Med Mol Imaging. 2011;38 Suppl 1:S69-77.
11. Bailey DL, Willowson KP. An evidence-based review of quantitative SPECT imaging and potential clinical applications. J Nucl Med. 2013;54(1):83-89.

12. Seret A, Nguyen D, Bernard C. Quantitative capabilities of four state-of-the-art SPECT-CT cameras. EJNMMI Res. 2012;2(1):45.

13. Kuwert, T. Skeletal SPECT/CT: a review. Clin Transl Imaging. 2014;2:505-517.

14. Ross, J.C., Vilić, D., Sanderson, T, Vöö S, Dickson J. Does quantification have a role to play in the future of bone SPECT? Eur J Hybrid Imaging. 2019;3:8.

15. Dickson, J., Ross, J. & Vöö, S. Quantitative SPECT: the time is now. EJNMMI Phys 2019;6:4.

16. Israel O, Pellet O, Biassoni L, De Palma D, Estrada-Lobato E, Gnanasegaran G, et al. Two decades of SPECT/CT - the coming of age of a technology: An updated review of literature evidence. Eur J Nucl Med Mol Imaging. 2019; 46(10): 1990-2012.

17. Mariani G, Strauss HW. Positron emission and single-photon emission imaging: synergy rather than competition. Eur J Nucl Med Imaging. 2011; 38(7):1189-1190.

18. van der Vos CS, Koopman D, Rijnsdorp S, Arends AJ, Boellaard R, van Dalen JA, et al. Quantification, improvement, and harmonization of small lesion detection with state-of-the-art PET. Eur J Nucl Med Mol Imaging. 2017;44(Suppl 1):4-16.

19. Tsui BMW, Zhao X, Frey EC, Gullberg GT. Comparison between ML-EM and WLS-CG algorithms for SPECT image reconstruction. IEEE Trans Nucl Sci. 1991;38:1766-1772.

20. Onoguchi M, Konishi T, Shibutani T, Matsuo S, Nakajima K. Technical aspects: Image reconstruction. Ann Nucl Cardiol. 2016;2:68-72.

21. Vija AH. Introduction to xSPECT technology: evolving multi-modal SPECT to become context-based and quantitative. In: Vija AH (ed) Molecular Imaging White Paper: Siemens Medical Solutions USA, , Molecular Imaging 2014.

22. Ma J, Vija AH. Evaluation of quantitation accuracy for xSPECT. Paper presented at:
Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC), 2015 IEEE, 2015. doi: 10.1109/NSSMIC.2015.7582030.

23. Duncan I, Ingold N. The clinical value of xSPECT/CT Bone versus SPECT/CT. A prospective comparison of 200 scans. Eur J Hybrid Imaging. 2018;2(1):4.

24. Delcroix O, Robin P, Gouillou M, Le Duc-Pennec A, Alavi Z, Le Roux PY, et al. A new SPECT/CT reconstruction algorithm: reliability and accuracy in clinical routine for non-oncologic bone diseases. EJNMMI Res. 2018;8(1):14.

25. Kuji I, Yamane T, Seto A, Yasumizu Y, Shirotake S, Oyama M. Skeletal standardized uptake values obtained by quantitative SPECT/CT as an osteoblastic biomarker for the discrimination of active bone metastasis in prostate cancer. Eur J Hybrid Imaging. 2017;1(1):2.

26. Willowson K, Bailey DL, Baldock C. Quantitative SPECT reconstruction using CT-derived corrections. Phys Med Biol. 2008;53(12):3099-112.

27. Tran-Gia, Lassmann M. Characterization of Noise and Resolution for Quantitative 177Lu SPECT/CT with xSPECT Quant. J Nucl Med 2019; 60:50-59

28. Armstrong IS, Hoffmann SA. Activity concentration measurements using a conjugate gradient (Siemens xSPECT) reconstruction algorithm in SPECT/CT. Nucl Med Commun. 2016;37(11):1212-1217.

29. Vija AH. Characteristics of the xSPECT Reconstruction Method. Siemens molecular imaging white paper. 2017.

30. Nakahara T, Daisaki H, Yamamoto Y, limori T, Miyagawa K, Okamoto T, et al. Use of a digital phantom developed by QIBA for harmonizing SUVs obtained from the state-of-the-art SPECT/CT systems: a multicenter study. EJNMMI Res. 2017;7(1):53.

31. Zimmerman BE, Cessna JT. Development of a traceable calibration methodology for solid $^{68}$Ge/$^{68}$Ga sources used as a calibration surrogate for $^{18}$F in radionuclide
activity calibrators. J Nucl Med. 2010;51(3):448-453.

32. Miyaji N, Miwa K, Wagatsuma K, Umeda T, Murata T, Takiguchi T, et al. Quality control of dose calibrator using a traceable syringe-type $^{68}$Ge/$^{68}$Ga calibration source. Nihon Hoshasen Gijutsu Gakkai Zasshi. 2013;69(12):1379-1386.

33. Miyaji N, Miwa K, Motegi K, Umeda T, Wagatsuma K, Fukai S, et al. Validation of Cross-calibration Schemes for Quantitative Bone SPECT/CT Using Different Sources under Various Geometric Conditions. Nihon Hoshasen Gijutsu Gakkai Zasshi. 2017;73(6):443-450.

34. Ichikawa H, Miwa K, Matsutomo N, Watanabe Y, Kato T, Shimada H. Development of a Novel Body Phantom with Bone Equivalent Density for Evaluation of Bone SPECT. Nihon Hoshasen Gijutsu Gakkai Zasshi. 2015;71(12):1235-1240.

35. Iida H, Hori Y, Ishida K, Imabayashi E, Matsuda H, Takahashi M, et al. Three-dimensional brain phantom containing bone and grey matter structures with a realistic head contour. Ann Nucl Med. 2013;27(1):25-36.

36. Kaneta T, Ogawa M, Daisaki H, Nawata S, Yoshida K, Inoue T. SUV measurement of normal vertebrae using SPECT/CT with Tc-99m methylene diphosphonate. Am J Nucl Med Mol Imaging. 2016;6(5):262-268.

37. Akamatsu G, Ikari Y, Nishida H, Nishio T, Ohnishi A, Maebatake A, et al. Influence of Statistical Fluctuation on Reproducibility and Accuracy of SUVmax and SUVpeak: A Phantom Study. J Nucl Med Technol. 2015;43(3):222-226.

38. Soret M, Bacharach SL, Buvat I. Partial-volume effect in PET tumor imaging. J Nucl Med. 2007;48(6):932-945.

39. Shinohara H, Hashimoto T. An Error Evaluation of Iterative Image Reconstruction Methods Using Chi-Square ($\chi^2$) Statistic Minimization for Poisson-Distributed Projection Data. Igaku Butsuri. 2018;38(3):113-128.
40. Okuda K, Fujii S, Sakimoto S. Impact of Novel Incorporation of CT-based Segment Mapping into a Conjugated Gradient Algorithm on Bone SPECT Imaging: Fundamental Characteristics of a Context-specific Reconstruction Method. Asia Ocean J Nucl Med Biol. 2019;7(1):49-57.

41. Matsutomo N, Matsumoto S, Yamamoto T, Sato E. Validation of a calibration method using the cross-calibration factor and system planar sensitivity in quantitative single-photon emission computed tomography imaging. Radiol Phys Technol. 2017;10(4):439-445.

Figures

Figure 1

Custom-designed phantom configured with vertebral body, spinous and transverse process, and a sphere set inside vertebral body to simulate bone metastasis.
Figure 2

We set the ROI80\% (red circle) at the center of xB image sample that based fusion axial image and then adjusted position by the sagittal and coronal image. (A), Fusion axial image; (B), Fusion sagittal image; (C), Fusion coronal image; (D), MIP image.
Reconstruction plots showing quantitative distribution in TBR1 (A), 2 (B), 4 (C) and 10 (D).

The filled and unfilled symbols indicate maximum and mean activity concentrations, respectively. The dotted line is the actual activity concentration of phantom. wishes, Flash 3D; xSPECT Quant; xSPECT Bone.
Figure 4

The FWHM measurement shown by the profile curve on the spinous process cross-section. (A), Spatial resolution of three reconstructions at various iterations. The dotted line is the actual size of the phantom. [], Flash 3D (F3D); [], xSPECT Quant (xQ); [], xSPECT Bone (xB). (B), A sample measurement of an xB image at 12 iteration numbers. (C), A measurement profile of an xB image at 12 iteration numbers.

Figure 5

Representative transaxial images of SPECT datasets including three reconstructions at TBR4. (A), Flash 3D (F3D); (B), xSPECT Quant (xQ); (C), xSPECT Bone (xB).
The coefficient of variance (CV) measurement in the ROI placed at the center of the vertebral body. (A), The CV as a function of iteration numbers. □, Flash 3D (F3D); □, xSPECT Quant (xQ); □, xSPECT Bone (xB). (B), A sample measurement of an xB image at 1 subset and 48 iterations.

The contrast-to-noise ratio (CNR) measured by activity concentrations for the hot spheres and normal bone at TBR 4. (A), The mean CNR as a function of iteration numbers. (B), The maximum CNR as a function of iteration numbers.
Figure 8

Recovery coefficients of three reconstructions at various numbers of iterations. The numbers of iterations in A, B, C, D, E and F are 12, 24, 36, 48, 60 and 96, respectively. In addition, the numbers of iterations in G and H show the different parameters of 36 and 48 in Flash 3D and 12 and 24 in xSPECT, respectively. □, Flash 3D (F3D); △, xSPECT Quant (xQ); ●, xSPECT Bone (xB).

Supplementary Files
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