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Title: Multicenter study of quantitative SPECT imaging: reproducibility of ^{99m}Tc quantitation using a conjugated gradient minimization reconstruction algorithm

Short Running Title: Reproducibility of SPECT quantification

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Abstract:

Objective: This multicenter study aimed to determine the reproducibility of quantitative single-photon emission computed tomography (SPECT) images generated by a commercially available, ordered-subset conjugate gradient minimization (OSCGM) reconstruction engine.

Methods: A common cylindrical phantom containing 100 kBq/ml technicium-99m (^{99m}Tc) pertechnetate solution in a volume of 7L of was scanned under standard imaging conditions at six institutions and under local clinical protocols at each. Inter-institutional variation was evaluated with the coefficient of variation (CV) among institutions in the quantitative SPECT images. The dose calibrator accuracy was also investigated by measuring the same lot of commercially available ^{99m}Tc vials.

Results: The respective radioactive concentrations under standard and clinical conditions ranged from 95.71±0.60 (mean ± standard deviation) to 108.35±0.36 kBq/mL, and 96.78±0.64 to 108.49±0.11 kBq/mL, respectively. The inter-institutional variation in the radioactive concentration was 4.20%. The bias in the radioactive concentrations in SPECT images was associated with each institutional dose calibrator accuracy.

Conclusion: We concluded that the reproducibility of the commercially available quantitative SPECT application using an OSCGM reconstruction engine was high, and comparable to that of positron emission tomography (PET), for comparatively large (~7L) homogeneous objects.

Key words

SPECT/CT, OSCGM, quantification, dose calibrator, ^{99m}Tc-MDP

Introduction

Single-photon emission computed tomography (SPECT) imaging has been considered less quantitatively accurate than positron emission tomography (PET) due to issues with sensitivity, spatial resolution, and various corrections including photon attenuation and scatter (*1-4*). The recent introduction of hybrid SPECT devices equipped with computed tomography (CT) capability has allowed not only lesion localization, but also more accurate quantitative assessment by correcting image-degradation factors (*1*, *5*). Several studies have suggested that standardized uptake value (SUV) of SPECT/CT is sufficiently accurate to have clinical value (*1*, *5-13*). Of note, Bailey et al. (*1*) reported that SPECT/CT quantitative accuracy is comparable to that of PET/CT.

Siemens Healthcare (Erlangen, Germany) introduced the xSPECT Quant™ to apply SPECT quantitation to clinical practice (*14*, *15*). For accurate quantification, xSPECT uses the CT coordinate system on its reconstruction to improve the alignment between SPECT and CT. The change of image formation space from a SPECT to a CT causes the increase of data volumes and its prolonged calculation time. To address this change, the xSPECT uses a unique reconstruction engine, namely an ordered-subset conjugate gradient minimization (OSCGM) algorithm, which has faster convergence compared to conventional ordered-subset expectation maximization (OSEM). The projection data unit is processed as count rates in OSCGM reconstruction. This concept differs from conventional count-based SPECT reconstruction, and it is similar to PET with voxel units of Bq/mL. Moreover, by calibrating the scanner to a reference source, the xSPECT Quant generates values for reconstructed SPECT voxels in units of radioactive concentration of Bq/mL. Sensitivity is regularly calibrated at a frequency of once every 30 days using a ^{57}Co standard point source

(or ^{99m}Tc) to maintain quantitative accuracy. Kuji et al. reported that the quantitative indices generated by xSPECT Quant are helpful for bone SPECT/CT imaging (*16*). According to previous studies that used a uniform phantom, the quantitative accuracy of xSPECT is 3% - 6% (*17*). The clinical value and quantitative accuracy of xSPECT have been reported as above, but reproducibility at several institutions has not yet been reported, to our knowledge. The present multicenter study aimed to determine the reproducibility of quantitative SPECT images generated by a commercially available application that uses an OSCGM reconstruction engine. To verify the inter-institution bias associated with the radioactivity measurements, the accuracy for dose calibrators was also evaluated.

Materials and Methods

Participating institutions

The Symbia Intevo (Siemens Medical Solutions USA Inc., Hoffman Estates, IL, USA) SPECT/CT system with a quantitative application based on an OSCGM reconstruction algorithm was installed at the six institutions that participated in the present phantom study. Table 1 summarizes the calibration sources and the sensitivity calibration factors (SCF) used at these institutions during phantom image acquisition. Two institutions measured the SCF using a ^{57}Co standard point source within 3% NIST-traceable accuracy. Others used ^{99m}Tc point sources created in house, whose radioactivity were measured with the individual dose calibrator certified by each manufacture within a year for the SCF measurements.

Phantom measurements

A uniform cylindrical phantom with a diameter of 21 cm (volume 6,810-mL), was set up by

removing all the internal features (cold spheres and cold rods) of a Jaszczak phantom (Data Spectrum Corp., Durham, NC, USA). The phantom was scanned at each institution to evaluate quantitative reproducibility. The concentrations of aqueous ^{99m}Tc solutions in the phantoms were adjusted using the dose calibrator at each institution to 100 kBq/mL with the pure water volume determined according to the measured radioactivity (~ 800 MBq). We used a graduated cylinder with a total volume of 1000 mL and accuracy of 2.0 mL to adjust solution volumes. SPECT scans were started immediately after the phantom filling. The radioactive decay of ^{99m}Tc was corrected in the SPECT quantification process, the radioactive concentration of output images was referenced to the measurement time of the radioactivity, from the central time of SPECT duration.

We conducted tests under two imaging conditions. Standardized study conditions were created to minimize variables and acquire phantom imaging data at each site. Thereafter, we assessed the potential inter-institutional variability of daily clinical practice by adopting the acquisition and reconstruction conditions used for bone SPECT imaging at each institution under routine clinical conditions. This is to mimic conditions used to routinely-generated clinical images. All SPECT images were acquired under the study conditions using a low-energy high-resolution collimator, 256 × 256 matrix and 2.4 mm pixel size. The energy window setting for ^{99m}Tc was 129.5 - 150.5 keV, and the scatter window setting was 108.5 - 129.5 keV. The cylindrical phantom was carefully located at the center of the field of view using CT positioning lasers. Phantom images were acquired from 72 projections over a 360° circular orbit with step-and-shoot acquisition, and the rotation radius of the detector was 260 mm. The time taken for each projection was adjusted to 20 sec, corresponding to a total acquisition duration of 12 min. X-ray computed tomography images were then acquired using

the parameters, 130 keV, 50 mA, tube rotation duration 0.6s, and pitch 1.0. The CT data were reconstructed with a slice thickness of 2.0 mm and a display field-of-view of 500 mm. Table 2 shows that modes of acquisition, projection numbers and the amount of time per view varied among institutions under the clinical conditions. The CT acquisition parameters were not standardized and inter-institutional variability persisted with respect to mA, slice thickness, and field-of-view settings.

Images were reconstructed using the OSCGM algorithm, integrating scatter correction using an energy window-based scatter estimation and attenuation correction according to an attenuation map derived from the CT data. The scatter estimation is modelled in OSCGM as part of the forward projection step in the reconstruction iteration. The details of OSCGM reconstruction are described elsewhere (*14*, *15*). The number of updates on OSCGM reconstruction under the common study conditions was set to 30 iterations per subset, which was based on the previous study (*17*), and was chosen to optimize the balance between the convergence for accurate quantification and the degradation of image uniformity. A Gaussian filter with a full width at half maximum of 6 mm was used for post smoothing. Table 2 shows that these reconstruction parameters varied among the institutions under the clinical conditions. In order to assess further variabilities introduced by differences in clinical routine, the optional reconstruction application adapted for bone SPECT, namely xSPECT Bone, was used at institutions A, C, E, and F. All reconstructed data units were generated in Bq/mL using the SCF measured at each institution.

Intra-institution reproducibility was examined at Institution A, in which the 2 Symbia Intevo SPECT/CT systems were installed. To get 6 data sets from one institution to complement the 6 data sets from 6 institutions, phantom filling and data acquisition were

repeated three times at separate days in each of two systems.

Dose calibrator accuracy

The measurement accuracy for dose calibrators was investigated using a commercially available ^{99m}Tc source, which had a same lot number and delivered to each institution from a manufacture facility (Nihon Medi-Physics Co. Ltd., Tokyo, Japan). Because the manufacture's dose calibrator is certified regularly with NIST traceable, it was assumed that the variations of the radioactivity and volume of ^{99m}Tc solution in the same lot were negligible, and we defined the operational true activity in the reference source as the measured value at the manufacture's factory (410.6 MBq in 1.13 mL at the assay date and time with the variation of ± 2%). The diameter of each glass vial containing ^{99m}Tc solution was 17.0 mm.

^{99m}Tc vial was measured at 5 time points over 3 days with the theoretical activity ranging from 615 MBq to 2 MBq using a dose calibrator available at each institution. In order to minimize the background radioactivity, each measurement was taken in the environment without any other radioactive sources or devices emitting radiowaves in the surrounding, after the dose calibrators had been turned on for sufficient warm-up time.

Data analysis

All SPECT images, acquired and reconstructed in individual institutions, were transferred to the central institution (Tottori University Hospital) in digital imaging and communications in medicine (DICOM) format, and analyzed using the OsiriX DICOM viewer version 5.6 (Pixmeo, Geneva, Switzerland). The mean radioactive concentration (kBq/mL) in five

circular regions-of-interest (ROI), drawn on consecutive slices in the center of the cylinder phantom were calculated. Each ROI encompassed about 80% of the interior diameter of the phantom (Fig.1). The results of measured radioactive concentration were expressed as mean ± standard deviation.

We evaluated reproducibility as the inter-institutional variation in the radioactive concentrations in SPECT images calculated using the formula:

$$\text{Variation}\ (\%) = \text{SD}/\text{mean} \times 100$$

where mean represents the mean radioactive concentration of acquired SPECT images and SD represents the standard deviation of the radioactive concentrations of the participating institutions.

The measurement accuracy in the dose calibrators test was calculated as the difference in radioactivity from the reference value as follows:

$$\text{Accuracy}\ (\%) = \left(\text{A}_{meas}/\text{A}_{ref} - 1\right) \times 100$$

where A_{meas} represents measured radioactivity at each of the participating institutions and A_{ref} represents the measured value at the manufacture's factory (410.6 MBq at the assay date and time).

Statistical analysis

Differences in reproducibility were compared between the two imaging conditions using Wilcoxon signed-rank tests and F-tests. Values with $p < 0.05$ were considered significantly different. All data were statistically analyzed using MATLAB R2013a (MathWorks Inc., Natick, MA, USA).

Results

The radioactive concentrations in SPECT images acquired under the common reconstruction and clinical conditions were 95.71±0.60 to 108.35±0.36 and 96.78±0.64 to 108.49±0.11 kBq/mL, respectively (Table 3). Inter-institutional variation under these two conditions were respectively 4.20% and 3.89%. Reproducibility did not significantly differ between the two imaging conditions ($p = 0.394$, Wilcoxon signed-rank test; $p = 0.893$, F-test). The results of intra-institution examination in Institution A are summarized in Table 4. The radioactive concentrations in SPECT images under study condition tested with 2 scanners repeatedly were 98.96±0.07 to 101.81±0.30 kBq/ml.

In Table 5, we show a measurement accuracy of dose calibrators within ± 5% from the manufacture's measurement obtained in most institutions. However, the measurement error in Institution F was relatively high (6.13 ± 0.44%). The measured values tended to be higher compared to the reference value, whereas Institution E underestimated.

Discussion

Quantitative SPECT images can be generated using a commercially available application, the clinical use of which is becoming more prevalent. The present multicenter study investigated the reproducibility of quantitative SPECT images generated using a commercially available application with an OSCGM reconstruction engine. The inter-institutional variation in the radioactive concentrations generated by xSPECT Quant was 4% under two study conditions. The results of PET studies are reported to show similar level of variability (*18*), suggesting that the quantitative reproducibility of xSPECT Quant in the homogeneous distribution of radiotracer throughout a relatively large (~7 L) volume is good

and comparable to that of PET (*1*,*13*).

Scanner variability and reconstruction parameters have been considered as technological factors affecting the accuracy of quantitative measurements in PET studies (*19*,*20*). The reproducibility of SPECT quantitation in the present study was good regardless of variability in imaging parameters. This might be associated with the cylindrical phantom. We selected this phantom to avoid errors due to the technical difficulties involved in phantom preparation at the participating institutions. One study that used a body phantom with spherical inserts found larger variation in quantitative values for small spheres (*21*). The object size and the difference in radiotracer is the major limitation in this study, since absolute measurements are often of most interest when applied to much smaller focal radiotracer uptake, and of special interest for the dosimetry of therapy agents (*22*). Because partial volume effects are influenced by the imaging conditions (*23*-*25*), the quantitative accuracy of xSPECT Quant requires further evaluation for smaller regions of interest that might be representative of focal uptake in a lesion, for example. Moreover, previous studies mentioned the quantitative values might be influenced by the noise characteristics in xSPECT Bone algorithm (*26*, *27*). The xSPECT Bone incorporated a weighted correction according to zone classification based on CT data. Our study design did not assess the effect of tissues zones used during reconstruction and our result of 3.89% of inter-institution variation in clinical protocol does not address the effect of zoning during reconstruction.

Dose calibrator accuracy and scanner calibration are also considerable factors in quantitative measurements (*19*, *20*). As the filled radioactivity in the phantom was measured with the dose calibrator equipped in each institution in this multicenter study, the dose calibrator bias had to be considered. By comparing Table 3 with Table 5, the measurement

accuracy of dose calibrator in each institution had direct impact on the bias in the radioactive concentration in SPECT images. For example, because the dose calibrator in Institution E was shown to underestimate the radioactivity compared to the calibrated value by the radiopharmaceutical manufacturer, the higher radioactivity might have been filled in the cylinder phantom prepared at this site. In short, the main cause for inter-institution variation in phantom study can be attributed to the variability in dose calibrator accuracy in the participating sites. This interpretation could be encouraged by the excellent intra-institution repeatability tested with identical dose calibrator in institution A. In addition to the intrinsic factors such as device calibration and electronic response, the radioactivity measurement of the dose calibrator depends on source shape, material, volume, and the surrounding (*28*-*31*). Our study used a commercially available ^{99m}Tc source with the same lot number to minimize variables. However, slight individual differences cannot be denied. Our study showed the general difference among six institutions in the measured radioactivity including the differences of manipulation and environment (e.g. shielding with lead material, or temperature and humidity), not only the intrinsic error of devices.

The unavailability of a common calibration source in the sensitivity calibration of the detectors was potential source of variability in our study. Miyaji et al. reported the SCF of the ^{99m}Tc source depended on the preparation method while the calibration using the ^{57}Co standard source is stable over a long period (*32*). Anizan et al. also mentioned that precise preparation and careful measurement of the calibration source activity and acquisition under negligible background radiation environment are required for the stability of planar-sensitivity based calibration (*33*). The effects of differences among calibration sources were not assessed in this study, hence we have no details about the variability.

Although the types of dose calibrators, calibration sources and other items differed among the participating institutions, the reproducibility of SPECT quantitation was sufficient to discuss quantitative uptake equally among multicenter. Our results indicated that xSPECT Quant harmonizes variability in a multicenter setting. However, the present phantom measurements were limited to a single radioactive concentration, and conducted only one measurement at each institute. The inter-institutional variability and accuracy of SPECT quantitation await future evaluation.

Conclusions

A commercially available quantitative SPECT application reproduced radioactive concentrations with an inter-institutional variation of 4.2%, which is comparable to PET for comparatively large (~7L) homogeneous object. This multicenter study is the first step towards the verification of SPECT quantitation and further investigation of accuracy is desirable. Nonetheless, our findings are significant in terms of clinical assessments of SUV using SPECT/CT.

Disclosure: The authors declare that they have no conflict of interest.

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Figure legends

FIGURE 1. Representative slice of cylindrical phantom. Grayed-colored circle indicates the placement of ROI on the phantom.

Tables

TABLE 1. Details of system sensitivity calibration at participating institutions.

Institution	**Calibration source**	**Sensitivity calibration factor [$s^{-1}MBq^{-1}$]**	
		Detector 1	**Detector 2**
A	^{99m}Tc	86.8	88.1
B	^{57}Co	88.2	88.7
C	^{99m}Tc	87.6	84.9
D	^{99m}Tc	89.9	85.3
E	^{57}Co	90.1	89.1
F	^{99m}Tc	87.7	88.2

TABLE 2. Bone SPECT image acquisition and reconstruction conditions used for clinical conditions at participating institutions.

Institution	**Acquisition**			**Reconstruction**	
	Mode	**Number of projections**	**Duration of projection [sec]**	**Updates (subsets)**	**Gaussian filter (full width at half maximum; mm)**
A	Continuous	90	12	48 (2)	5
B	Step & Shoot	120	10	30 (1)	6
C	Continuous	90	12	48 (2)	10
D	Continuous	120	9	30 (1)	7
E	Step & Shoot	72	20	48 (2)	5
F	Continuous	72	16	40 (1)	7

TABLE 3. Radioactive concentrations in SPECT images under two conditions at participating institutions.

Institution	**Radioactive concentrations in SPECT images (kBq/mL)**	
	Study condition	**Clinical condition**
A	99.65±0.24	102.29±0.55
B	99.32±0.40	99.90±0.25
C	101.33±0.36	103.77±0.51
D	102.96±0.37	104.09±0.24
E	108.35±0.36	108.49±0.11
F	95.71±0.60	96.78±0.64

TABLE 4. Radioactive concentrations in SPECT images in the repetitive experiment in Institution A.

Scanner	Radioactive concentrations in SPECT images (kBq/mL)		
	Test 1	**Test 2**	**Test 3**
1	98.96±0.07	100.58±0.86	100.01±0.51
2	99.65±0.24	101.53±0.22	101.81±0.30

TABLE 5. Measurement accuracy for each institutional dose calibrator.

Institution	**Dose calibrator**	**Accuracy [%]**
A	IGC-7E	1.68 ± 0.42
B	IGC-7	1.95 ± 0.76
C	CRC-55tW	1.82 ± 0.69
D	IGC-7	4.54 ± 0.39
E	ATOMLAB 500	-4.90 ± 0.21
F	IGC-7F	6.13 ± 0.44

Graphical abstract