Original

The Influence of Attenuation and Scatter Corrections on Quantitative Analysis of ^{123}I–FP–CIT SPECT Brain Imaging

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ABSTRACT

Objective: [^{123}I] N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-[^{123}I]iodophenyl) nortropane (^{123}I-FP-CIT) or dopamine transporter (DAT) SPECT scan quantitatively depicts striatum dopamine transporter density. The specific binding ratio (SBR) is important for Parkinson's disease (PD) diagnosis. Correction techniques may improve ^{123}I-FP-CIT image quality, but they are currently not standardized. We aim to determine attenuation correction (AC) and scatter correction (SC) influence on ^{123}I-FP-CIT quantitative analysis.

Methods: We preformed SPECT imaging on a striatal phantom representing striatum-to-background ratios ranging from 10:1 to 1:1. We used the Chang method for AC and triple energy window for SC. Commercially available software semi-automatically calculated SBR. We performed correlation analysis between SBR and the actual concentration ratio in four groups: no correction (NC), SC, AC, and combined correction (CC), paying particular attention to SBR values below the clinical cut-off (4.5). We applied the same imaging conditions, reconstruction, and corrections on 49 human ^{123}I-FP-CIT SPECT studies. Asymmetric index values (AI) were also analyzed. Receiver operating characteristic (ROC) analysis provided AI diagnostic cut-off values in PD patients. PD patient population whose AI values were above these cut-off value were subject to a correlation study to confirm the association between their clinical symptoms and ^{123}I-FP-CIT SPECT.

Results: *Phantom study.* AC or CC increased SBR ^{123}I-FP-CIT SPECT, making them very close to the standard ratios (AC: $y=1.19x-0.7$; $R^2=0.98$; CC: $y=1.4x-1.2$; $R^2=0.98$), while NC and SC underestimated SBR at lower values (1 to 4). *Clinical study.* There was no difference in SBR between NC and SC, while AC and CC produced significantly higher SBR than NC ($p<0.0001$). Only SC affected AI values ($p<0.05$). The association between clinical symptoms and ^{123}I-FP-CIT imaging results were maintained only when either NC (n=12, $p<0.05$) or CC (n=14, $p<0.05$) was applied.

Conclusions: AC increased SBR more than other corrections, while SC increased AI value more than other corrections. The association between clinical symptom and SPECT findings were maintained when either NC or CC was applied. These correction methods should be carefully selected for ^{123}I-FP-CIT SPECT brain imaging.

Article Information

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Introduction

A meta-analysis study showed that in a population over 40 years old, approximately 37 females per 100,000 and 61 males per 100,000 are at risk of Parkinson's disease (PD).[1] The incidence of PD steadily increases with age, to peak between ages of 70 to 79.[2] Diagnosis of PD based on clinical symptoms is complicated because PD has a broad spectrum of motor and non-motor symptoms. Another difficult aspect of PD diagnosis is that patients show motor symptoms only after about 60% of dopaminergic neurons are lost.[3] By that time (which is also when conventional imaging modalities can diagnose the disease), any neuroprotection approach would be too late. Early detection of PD is a key factor in slowing disease progression, preserving neurophysiological integrity of neurons, improving the patient's quality of life, and reducing the burden on financial and human resources.

Advanced neuroimaging such as dopamine transporter (DAT) scan can be useful for the definitive diagnosis of PD. Measurement of DAT density allows evaluation of dopamine production in the presynaptic terminal. Among DAT-related imaging agents used in PET and SPECT, ^{123}I FP-CIT (N-(3-Fluoropropyl)-2β -carbomethoxy-3β-(4-[^{123}I]iodophenyl) nortropane) is the most commonly used due to its high affinity for striatal DAT. ^{123}I-FP-CIT SPECT is reported to be useful in detecting degeneration of the dopaminergic nigrostriatal pathway, distinguishing between essential tremor and presynaptic Parkinson's syndromes, and differentiating PD from other forms of Parkinsonism.[4]

Interpretation of ^{123}I-FP-CIT SPECT is based on visual evaluation with the aid of quantitative analysis. Although visual assessment is accepted in clinical practice, it is highly dependent on the nuclear medicine physician's experience. Quantification is necessary for ^{123}I-FP-CIT SPECT to substantiate accurate diagnosis. Several studies have shown that quantitative assessment of ^{123}I-FP-CIT SPECT enables detection of subtle changes, leading to early disease detection, and is also valuable in patient follow-up.[4-6] For quantification of ^{123}I-FP-CIT SPECT, the striatal binding ratio (SBR) is calculated by comparing the activity in the striatum (due to specific binding) and the activity in the background or reference area (usually the occipital area or cerebellum, reflecting non-specific binding). As is any other radioisotope imaging technique, ^{123}I-FP-CIT is prone to attenuation and scatter. However, the usage of correction techniques to address these issues is currently not standardized.

There have been several studies investigating the effect of attenuation correction (AC) and scatter correction (SC) on quantitative ^{123}I-FP-CIT SPECT. Vines *et al.* and Kim *et al.* showed in phantom studies that SC resulted in significant improvement not only in qualitative evaluation but also in quantitative analysis.[7,8] In another phantom study, Rajeevan *et al.* reported that AC moderately improved the accuracy of absolute activity in the striatum and background.[9] A multicenter study on phantoms and patients using ^{123}I-FP-CIT SPECT demonstrated that diagnostic accuracy of visual interpretation of ^{123}I- FP-CIT SPECT did not depend on AC.[10] However, Warwick *et al.* studied phantoms and 14 patients and showed that AC improved the quantitation of striatal SPECT images of the phantom, and AC also optimized patients' brain SPECT reconstruction.[11] Another parameter in interpreting ^{123}I-FP-CIT SPECT is the asymmetric index (AI) value to evaluate the asymmetry of radioligand uptake.[12]

The aim of this study was to evaluate the influence of AC and SC on the quantitative analysis of ^{123}I-FP-CIT SPECT brain imaging in both phantom and clinical studies.

Materials and Methods

Phantom study

SPECT imaging was performed on an acrylic anthropomorphic phantom (DaT1308, Nihon Medi-Physics Co., Ltd., Tokyo, Japan). This phantom consists of two compartments: 1) striatal compartments (striatum) and 2) brain shell cavity. The phantom was filled with β -methyl-p-[^{123}I]iodophenyl-pentadecanoic acid (^{123}I-BMIPP) to obtain striatum-to-background concentration ratios of 10, 8, 7, 5, 4, 3, 2.5, 1.25, and 1 to 1, respectively. These ratios were defined as the standard ratios. The phantom was initially filled with a ratio of 10:1, by filling the caudate and putamen with 55.5 kBq/ml and the brain shell cavity with 5.64 kBq/ml ^{123}I-BMIPP solution, and imaged. Subsequently, the striatal chambers were then emptied, flushed, and refilled with a diluted concentration of the ^{123}I solution for the next set of images.

Patient preparation

Forty-nine consecutive patients who had ^{123}I-FP-CIT SPECT brain imaging between April and October 2016 were enrolled in this retrospective study. The protocol of this study was approved by the Ethics Committee of Gunma University (No. 2018-110). Patients were administered 167 MBq of ^{123}I-FP-CIT (^{123}I-Ioflupane, DaTSCAN, Nihon Medi-Physics Co., Ltd., Tokyo, Japan), and SPECT images were acquired three hours after injection. Patients did not undergo any special preparation before the scan.

SPECT acquisition

A dual-headed SPECT with low-and-medium energy general purpose (LMEGP) collimator (Toshiba E.cam Signature series; Toshiba Medical Systems, Tochigi, Japan) was used in both phantom and patient studies. The SPECT data were acquired by using dynamic tomography of 2 repeats, 4 cycles/repeat, 210 s/cycle on a 128×128 matrix, zoom 1.45, and an energy window of 159 keV (±20%). Two detectors rotated 360° around the subjects. The rotation radius was adjusted so that the distance bet-ween detectors and subjects was as small as possible. Emission data were reconstructed by using ordered subset expectation maximization (OSEM) with 6 subsets and 8 iterations. Pixel size of axial slices was 3.3×3.3 mm.

Image correction methods

SC was performed by using triple energy windows (TEW) in which the main window was at the peak of 159 keV±20%, and two additional windows for scatter correction (159 keV±7%). OSEM Chang method was used for AC in which the boundary was fixed in the brain, and the attenuation coefficient was $\mu = 0.14\ cm^{-1}$. We used OSEM with 6 subsets and 8 iterations for Chang AC instead of the filtered back projection (FBP) method as usually seen in clinical practice.

The data were reconstructed as four groups to compare the effect of AC and SC: 1) no correction (NC), 2)

SC, 3) AC), and 4) combined correction (CC). In the phantom study, all the above data were compared to the standard ratio. In the clinical study, NC represented the reference method, as it is common in clinical practice.

Quantitative analysis

All reconstructed data were imported into DATview software (Nihon Medi-Physics Co., Ltd., Tokyo, Japan) for automatic calculation of SBR and asymmetric index (AI). ROI selection was based on the two-box method developed by Tossici-Bolt, *et al.*,[13] which use this formula to calculate SBR:

$$\mathrm{SBR} = \frac{1}{\mathrm{Vs}}\left(\frac{\mathrm{CtVOI}}{\mathrm{Cr}} - \mathrm{VVOI}\right)$$

in which: Ct_{VOI}, total counts in the striatal volume of interest (VOI),
C_r, total counts in reference area,
V_{VOI}, volume of striatal VOI,
Vs, known volume of striata from reference (11.2 mL).

AI value was calculated to evaluate the striatal asymmetry of radioligand uptake. Basically, the AI value is the ratio of left and right SBR, which is estimated by the following formula [12]:

$$\mathrm{AI\ value} = 200\% \times \frac{\mathrm{Abs}\,(\mathrm{SBRright} - \mathrm{SBRleft})}{\mathrm{SBRright} + \mathrm{SBRleft}}$$

in which Abs is an absolute value, and SBR_{right} and SBR_{left} are the specific binding ratios of right and left striata calculated by DAT view software.

Patients who had $SBR < 1$ were excluded from AI value analysis ($n=3$) since they had abnormally high AI value.

Statistical analysis

Each group was compared to the standard reference. Receiver operating characteristic (ROC) analysis was performed in PD patients ($n=22$) with laterality symptoms to obtain optimal diagnostic cut-off for AI value. PD patients whose AI values were above the cut-off were further analyzed with chi-square test for association between clinical symptoms and imaging findings. A *p*-value of 0.05 was considered the limit of significance level. Statistics were performed with IBM SPSS Statistics (version 23, IBM Corp., Armonk, NY).

Results

Phantom study

Without any correction (NC), the SBR was underestimated ($y=1.0451\times-1.8083$, $R^2=0.9824$) compared with standard ratios ($y=x$). The underestimation also occurred when SC was used ($y=1.2426\times-2.3393$, $R^2=0.9769$). With AC or CC, the SBR was closer to the standard ratios (AC: $y=1.1884\times-0.6851$, $R^2=0.9826$; CC: $y=1.397\times-1.1809$, $R^2=0.9818$), in particular, at low SBR values (1 to 4), as shown in Fig. 1. Representative axial phantom scan slices, shown in Fig. 2 (a-d), showed the effect of AC, SC and CC on striatal compartment and background.

Clinical study

Table 1 showed the characteristics of patients enrolled in our study. The final diagnosis was based on neurologists' diagnoses. The SBR values were shown in Table 2. While SC did not change SBR significantly ($p=0.121$), AC and CC increased SBR significantly ($p<0.000$) (Fig. 3a). This finding confirmed our phantom study results. Corrections affected AI differently. SC raised the AI value significantly ($p<0.05$), while AC and CC did not change the AI value (Fig. 3b). AI values are shown in Table 2.

Typical clinical images are shown in Fig. 2(e-h). ROC analysis results are shown in Table 3. ROC analysis was carried out to evaluate the diagnostic value of AI value for clinical symptoms (laterality) in all PD patients ($n=22$). AI values obtained from NC method had both highest sensitivity and specificity in diagnosing laterality. Association between clinical symptoms and

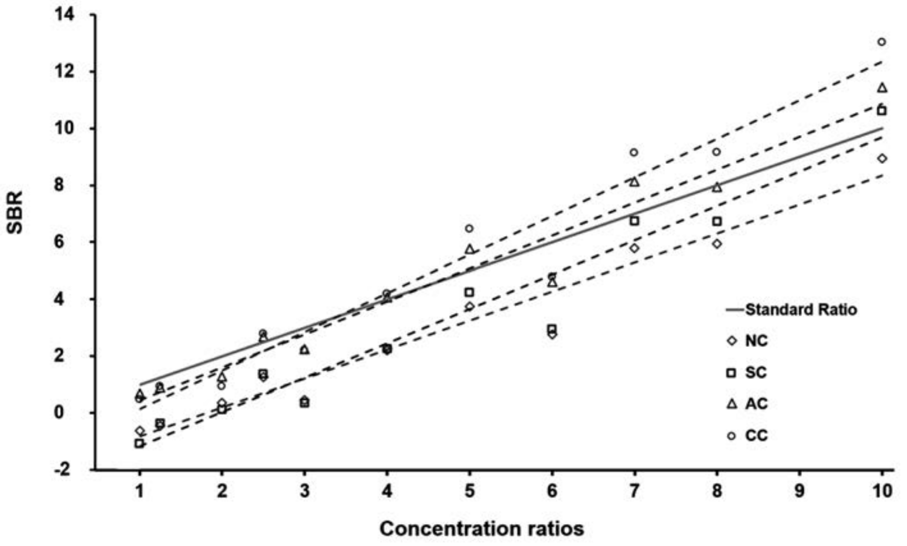


Fig. 1 Correlation between standard ratio and SBR (striatal binding ratio) in phantom study.

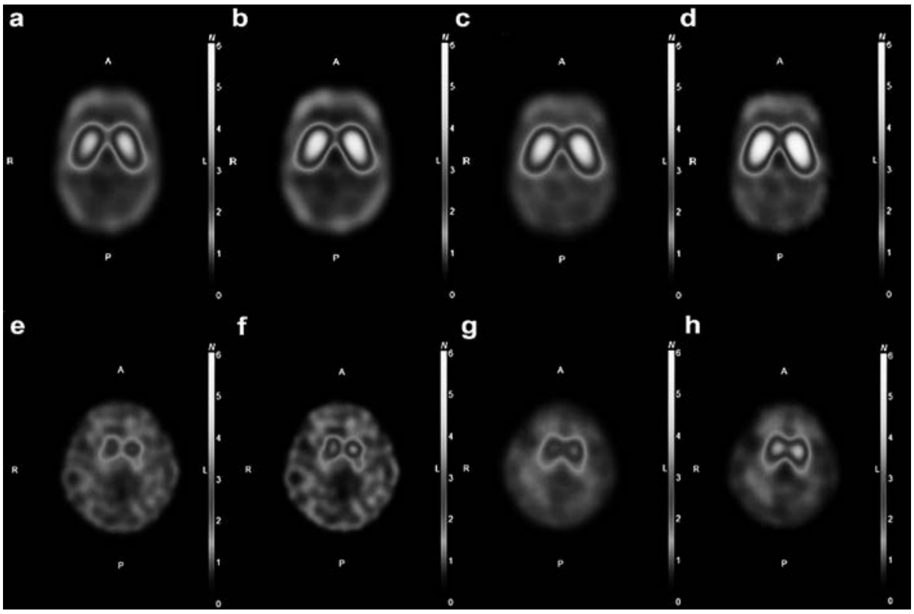


Fig. 2 Representative axial scan slice images from phantom study striatal binding ratio with standard ratio of 7:1 and clinical study (e-h) of 63 year-old female PD patient [e. NC (SBR, AI; 2.8, 5.7%); f. SC (3.55, 9.6%); g. AC (4.65, 5.1%); h. CC (6.11, 15.4%)].
* PD; Parkinson's disease, NC; no correction, AI; asymmetric index value, SC; scatter correction, AC; attenuation correction, CC; combined correction.

Table 1 Patients' characteristics.

Characteristics	Patients (n=49)
Number of examinations	51
Median age, range	70.38±9.33 (40－86)
Sex	
Male	15
Female	34
Final diagnosis	
PD	22
DLB	3
PSP or ALS	5
MSA	5
No PD	5
ET	3
Drug PD	1
Unclear	5

PD: Parkinson's Disease, DLB: Dementia with Lewy bodies, PSP: Progressive supranuclear palsy, ALS: Amyotrophic Lateral Sclerosis MSA: Multiple System Atrophy, ET: Essential Tremor

Table 2 SBR and AI value results from all patients.

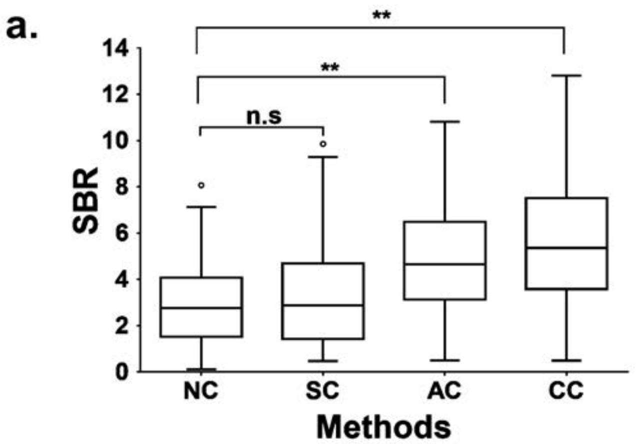
SBR (n=51)	NC	3.00 ± 1.77 (0.11-8.07)
	SC	3.43 ± 2.25 (1.12-9.86)
	AC	4.97 ± 2.24 (0.5-10.81)
	CC	5.71 ± 2.59 (0.49-12.52)
AI value (n=48)	NC	17.80 ± 19.80 (0.2-77.7)
	SC	21.60 ± 19.75 (8.9-61.4)
	AC	15.63 ± 16.18 (9.0-48.0)
	CC	14.74 ± 12.66 (2.1-41.2)

Data are a mean value±standard deviation, with a range in parentheses.
* SBR; striatal binding ratio, AI; asymmetric index value, NC; no correction, SC; scatter correction, AC; attenuation correction, CC; combined correction.

Table 3 ROC analysis of AI value for NC, SC, AC, and CC

Correction Method	AUC	AI cut-off values	Sensitivity	Specificity	Association*	
					p value	Chi-square
NC	0.861	13.0%	83.3%	83.3%	0.028	4.80
SC	0.729	18.7%	85.7%	60.0%	0.074	3.20
AC	0.615	9.4%	80.0%	44.4%	0.247	1.34
CC	0.736	14.5%	78.6%	70.0%	0.040	4.20

* performed in PD patients whose AI value above the cut-off (NC, n=12; SC, n=16; AC, n=17; CC, n=14). ROC; receiver operating characteristic, AUC; area under the curve.



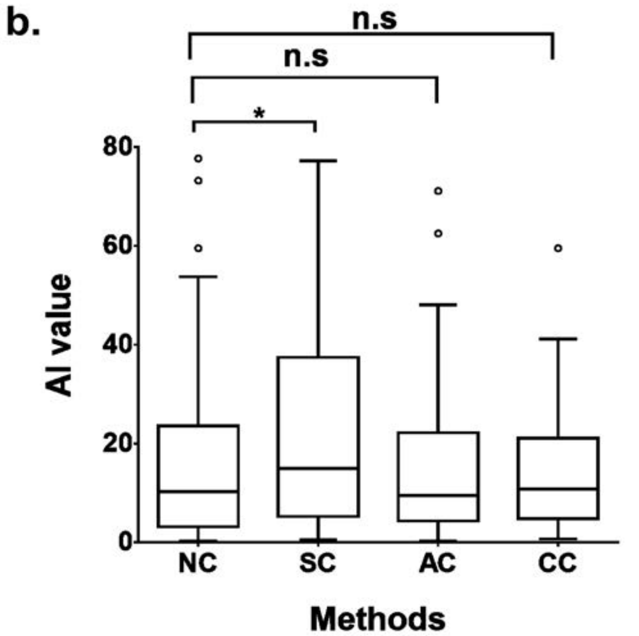


Fig. 3 Effects of each correction method on (a) SBR ($n=51$) and (b) AI ($n=48$) in clinical studies. * $p<0.05$, ** $p<0.0001$, n.s; not significant.

AI value above the cut-off was significant when NC or CC was applied ($p<0.05$).

Discussion

[123]I-FP-CIT SPECT is valuable in detecting nigrostriatal cell loss at the premotor stage of PD patients. In a longitudinal [123]I-β-CIT SPECT (an older tracer with slower striatal uptake) study on patients with Parkinsonian syndromes, SBR was rapidly reduced 42% during a short period in Parkinson's disease patients, compared to the slow reduction in aged-corrected normal values.[14] Quantitative assessment is likely to be similarly useful in supporting visual interpretation in [123]I-FP-CIT SPECT. Quantification in [123]I-FP-CIT SPECT is based on SBR, which is basically a count ratio between the striatum and the background. Count uptake is affected by attenuation and scatter in all types of radioisotope imaging. Corrections are commonly made in nuclear medicine to improve the accuracy of the count uptake.

In this study, we found that AC had a greater effect on the SBR than SC. There are several studies evaluating the effect of AC and SC on [123]I-FP-CIT SPECT quantification. These studies generally obtained, SBRs from ROIs covering the striatum and a limited background area (occipital cortex or the cerebellum only). In our study, we used an extended ROI selection method as developed by Tossici-Bolt *et al.* which aimed to minimize manual intervention and to take into account partial volume effect.[13] The main improvement from the other ROI drawing methods was the inclusion of the whole brain parenchyma as a reference, instead of only the occipital area. For attenuation correction using the Chang method, previous quantitative [123]I-FP-CIT SPECT studies often employed FBP reconstruction, while our study used OSEM reconstruction.

In our phantom study, we found that applying SC or not applying any correction would similarly underestimate SBR, while applying AC and CC increased SBR so that it was considerably closer to the standard ratios. The tendency in SBR change was the same in our clinical study in that SBR increased significantly after AC and CC, but not when SC or NC was applied. However, no standard ratio is available in human studies, so we do not know whether this SBR increase improves or worsens accuracy.

When AC was applied, SBR increased due to the presumed photon increase. When SC was applied, SBR increased due to the presumed reduced scatter. Our findings showed that when combined, the AC affected SBR more than SC did. A previous phantom study by Kim *et al.* showed that CC underestimated the activity in the striatum by 7.3% and AC underestimated it by 31.9%.[7] They also confirmed this finding in six human subjects, in which the SBRs from CC were higher than the SBR with AC. Vines *et al.* reported that SC resulted in significant SBR improvement compared with the standard ratios of their phantom (only 3.3% lower than the standard ratios).[8] However, these results were calculated using counts of activity uptake in the striatal compartment and occipital lobe only.

Although FBP has been commonly used with Chang AC, in our study, we applied the OSEM method. Iterative reconstruction methods enhance reconstructed image quality better than FBP reconstruction, especially in cases with relatively poor data (low counts with high noise).[15] Moreover, the OSEM method reduces the star artifact caused by FBP, hence increasing count.[16] Maebatake *et al.* showed that when [123]I-FP-CIT SPECT was acquired with LMEGP collimator, SBR mean and SBR max were significantly lower with FBP than with OSEM, ($47.7\pm1.0\%$ compared to $69.7\pm4.2\%$ in SBR mean, and $74.3\pm7.2\%$ compared to $130.6\pm8.3\%$ in SBR max).[17] In our study, we did not compare the effect of FBP with that of OSEM. However, the considerable SBR increase when AC was applied might be due to the effect of OSEM on AC.

The previous SBR cut-off for clinical diagnosis was 4.5.[13] Our study demonstrated that application of AC would potentially underestimate disease if this cutoff is used, since AC will significantly raise the SBR. However, a recent Japanese study conducted on healthy Japanese volunteers (n=19) evaluating the quantitative reference value of ^{123}I-FP-CIT SPECT reported a normal SBR range mean of 5.31±1.04 (without AC) and 6.84±1.01 (with AC).[18] Given this new evidence, application of AC might be reliable, but some caution might be needed.

AI value is an important parameter in ^{123}I-FP-CIT SPECT. Increased AI value can be very beneficial in detecting mild changes found in the disease during its early stages.[19] AI value is a useful parameter for differentiating vascular Parkinsonism from PD.[12] Contraffato *et al.* showed that AI value could be used to predict the short-term responsiveness to L-dopa in PD patients, in which the mean absolute AI value was 19.1±11.8.[20]

In our study, the mean of AI value of PD patients (n=21) was 20.43±21.31 when NC was applied. When SC, AC, and CC were applied, mean AI values were 26.2±19.6, 19.0±17.1, and 15.14±11.4, respectively. Lange *et al.* reported an AI value of 15.92±12.94 when SC was applied.[10] Bieńkiewicz *et al.* reported that when AC was used, the mean of AI value was 15 in patients with abnormal ^{123}I-FP-CIT SPECT.[21]

Based on the association between AI value and clinical symptoms (laterality) in PD patients, we found that NC might provide the most accurate AI value. The cutoff AI value of 13% obtained in this study might have a quantitative role in the interpretation of ^{123}I-FP-CIT SPECT. This association was also meaningful when both correction methods were applied. However, the accuracy was not as high as when NC method was used.

Our finding suggest that AC might affect SBR more than SC. Therefore, it should be applied with discretion. SC may be applied more liberally, since it does not significantly affect the SBR. SC might also help intensify uptake laterality by increasing AI value, which might be particularly useful in patients who are clearly symptomatic but have borderline (i.e. low AI value) images. However, we found no significant association between PD patients' symptom laterality and AI value obtained from the SC method. This suggests that SC might lack clinical significance. Further studies with a larger number of patients are necessary to confirm these findings.

In this study, we used dynamic tomography (to yield more counts), evaluated both correction methods, used the better registration method (OSEM vs FBP), improved the ROI drawing method, and performed experiments on both phantom and clinical cases. However, our results showed that even though correction methods might theoretically improve the qualitative and quantitative role of ^{123}I-FP-CIT SPECT in PD diagnosis, this potential improvement was not clearly observed, and these techniques might, in fact, have no clinical benefit. Thus, any correction method, if necessary, should be applied only after very careful consideration. .

The limitations of this study were: 1) in the phantom study, standard ratio was obtained only from one experiment (to reduce radiation exposure from ^{123}I), which might not be adequate to produce a statistically robust standard ratio, and 2) the number of patients was small.

Conclusion

AC increased SBR more than other corrections, while SC increased AI value more than other corrections. However, based on the association between AI value and clinical symptoms, leaving the image uncorrected might be the best option. AI value cut-off of 13% of uncorrected image might clearly discriminate PD patients with ^{123}I-FP-CIT SPECT -confirmed laterality symptoms.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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