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Evaluation of breath-hold ^{201}Tl SPECT in the differential diagnosis of solitary pulmonary nodules

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The aim of this study was to evaluate the usefulness of deep inspiration breath-hold SPECT (BrST, a method for ^{201}Tl SPECT) in the diagnosis of solitary pulmonary nodules (SPN). ***Methods:*** Ten patients with malignant lesions and five with benign lesions were enrolled in this study. Early SPECT acquisition was performed 15 min after injection of ^{201}Tl, while delayed SPECT images were acquired 3 h after injection. The first 15-sec acquisition was done using the BrST technique, and the second with the conventional free breathing (FB) method. We performed this technique alternately, and therefore, the odd data were from BrST and the even data were from FB. We referred to the T/N ratio of the early images as the ER and to the T/N ratio of the delayed images as the DR. To semi-quantitatively evaluate the degree of retention in the lesion, the retention index (RI) was calculated. ***Results:*** The RI of BrST indicated greater accuracy than that of FB in the differential diagnosis of SPN. For the benign and malignant lesions, the RI of BrST was −3.07 ± 31.51 and 29.86 ± 25.01, respectively ($p < 0.05$). The sensitivity, specificity, and accuracy of BrST (80%, 80%, and 80%, respectively) were significantly higher than those of FB ($p < 0.05$). ***Conclusion:*** The BrST method is more accurate than that of the conventional FB method in the differential diagnosis of SPN.

Key words: thallium-201, solitary pulmonary nodule, breath-hold

INTRODUCTION

Single-photon emission computed tomography using thallium-201 (^{201}Tl SPECT) is as useful as 2-[fluorine-18] fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) for differentiating benign from malignant lesions in the patients with solitary pulmonary nodules (SPN).[1–3] However, it is difficult to evaluate small SPN less than 2 cm with ^{201}Tl SPECT.[4] The aim of this study was to evaluate the usefulness of deep inspiration breath-hold SPECT (BrST, a method for ^{201}Tl SPECT) in the differential diagnosis of SPN. The retention index (RI) of ^{201}Tl SPECT is useful in differentiating benign from malignant lesions in SPN, but the respiratory effect can not be avoided in the conventional free breathing (FB) method of ^{201}Tl SPECT. Therefore, we developed a deep inspiration BrST method for ^{201}Tl SPECT, and examined the early uptake ratio (ER), delayed uptake ratio (DR), and RI in patients with SPN.

MATERIALS AND METHODS

Patients

Fifteen patients (10 men and 5 women, mean age: 68.0 ± 9.0 yr) with pulmonary nodules were enrolled in this study between March 2003 and February 2004. None of the patients had received chemotherapy before this study. There were 9 patients with non-small cell lung carcinomas, 1 with bronchioloalveolar cell carcinoma, and 5 with benign lesions (Table 1). The mean short axis of SPN was 22.7 ± 13.2 mm. The SPN were located in the upper lobe

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Table 1 The patients' characteristics and radionuclide imaging results

Patient no.	Age (yr)	Sex	Histologic type	Location	Size (mm)	BrST			FB		
						ER	DR	RI	ER	DR	RI
1	54	F	BAC	LML	24 × 20	3.75	2.88	–23.2	4	1.82	–54.5
2	66	M	non-small	LUL	18 × 18	1.64	2.44	48.8	1.35	1.67	23.7
3	72	M	non-small	RUL	53 × 40	2.75	4.3	56.4	2.93	3.73	27.3
4	74	F	non-small	RLL	50 × 33	5.91	7.79	31.8	5.87	8.34	42.1
5	65	M	non-small	RLL	12 × 10	2.11	2.47	17.1	NA	NA	NA
6	68	M	non-small	LUL	52 × 52	5.35	6.8	27.1	6.15	6.72	9.3
7	68	M	non-small	RUL	32 × 32	1.63	2	22.7	1.66	2.01	21.08
8	64	F	non-small	RUL	12 × 30	1.36	2.14	57.4	1.58	2.02	27.8
9	57	M	non-small	RML	23 × 14	1.63	1.85	13.5	1.12	1.48	–24.3
10	75	M	non-small	RLL	53 × 39	3	4.52	50.7	3.24	4.25	31.2
11	69	M	tuberculoma organized	LUL	30 × 12	3.53	3.39	–3.97	4.41	3.88	–12
12	70	M	pneumonia	RUL	30 × 23	1.69	2.32	37.3	1.41	2.17	53.9
13	83	M	CIC	LUL	30 × 12	2.16	1.72	–20.4	2.27	1.62	–28.6
14	73	F	CIC	LLL	17 × 13	4.65	2.6	–44.1	4.14	2.5	–39.6
15	63	F	CIC	RUL	16 × 11	1.9	2.2	15.8	1.97	2.3	16.8

BrST = breath-hold SPECT; FB = free breathing; ER = early ratio; DR = delayed ratio; RI = retention index; BAC = bronchioloalveolar cell carcinoma; non-small = non-small cell lung cancer; CIC = chronic inflammatory change; LML = left lower lobe; LUL = left upper lobe; RUL = right upper lobe; RLL = right lower lobe; NA = no accumulation

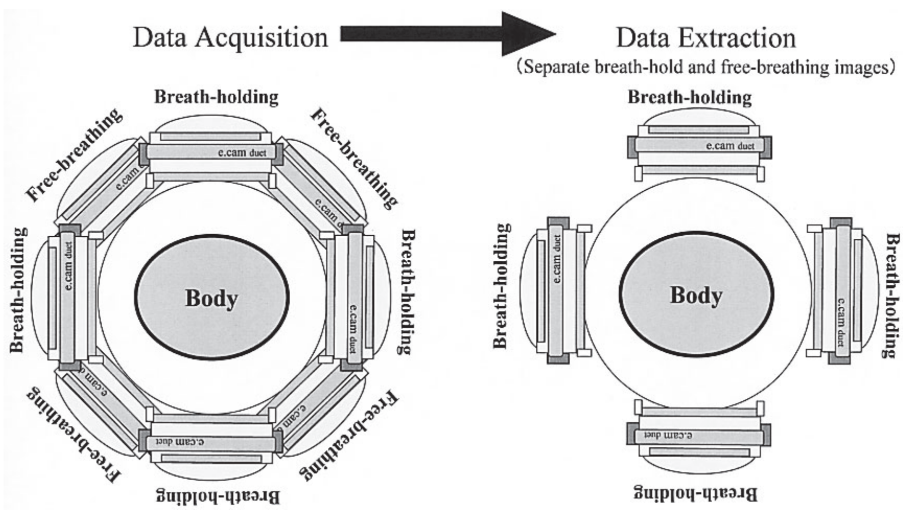

Fig. 1 Illustration of the breath-hold SPECT (BrST) method. The breath-hold and free-breathing data were acquired in alternate views, and the breath-hold views were extracted after acquisition.

(9 lesions), middle lobe (2 lesions), and lower lobe (4 lesions). Diagnosis was made by cytological or histopathological analysis of the sputum, CT-guided needle biopsy specimens or endoscopic samples. After the purpose of the study had been explained, all patients gave their informed consent.

The BrST method for ^{201}Tl SPECT

^{201}Tl chloride at 111 MBq was injected intravenously. The early SPECT acquisition was performed 15 min after injection of ^{201}Tl, while the delayed SPECT images were acquired 3 h after injection. For SPECT images of the chest, 60 projections over 360-degree were obtained using a 128 × 128 matrix at 15 sec per view using dual-head rotating gamma cameras (e-cam duet; Toshiba, Tokyo, Japan) equipped with a low-energy high-resolution collimator. The slice thickness was 3.9 mm. A series of transverse slices was reconstructed with filtered back-projection using a Ramachandran with a cutoff frequency of 0.51 cycle/pixel. No attenuation correction was performed. We divided 120 projections over 360-degrees into BrST and FB. The other procedures in the FB method were the same as those in the BrST method.

The first 15-sec acquisition was done using the BrST method, and the second with the conventional FB method. We performed this technique alternately, and therefore, the odd data were from BrST and the even data were from FB. Our technique acquired deep breath-hold and free-

Table 2 The early ratios, delayed ratios, and retention index for the BrST and FB methods in benign and malignant lesions

	BrST		FB	
	Benign	Malignant	Benign	Malignant
ER	2.79 ± 1.27	2.91 ± 1.62	2.84 ± 1.35	3.10 ± 1.91
DR	2.45 ± 0.62	3.71 ± 2.11	2.49 ± 0.84	3.56 ± 2.48
RI	−3.07 ± 31.51	29.86 ± 25.01*	−1.90 ± 37.75	11.52 ± 31.07

*p < 0.05 as compared with the corresponding FB group (Student's t-test)
BrST = breath-hold SPECT; FB = free breathing

Table 3 The ROC curve analysis results

	BrST			FB		
	ER	DR	RI*	ER	DR	RI
Sensitivity (%)	60	70	80	55.6	44.4	66.7
Specificity (%)	40	60	80	60	80	80
Accuracy (%)	53.3	66.7	80	57.1	57.1	71.4
AUC	0.44	0.66	0.80	0.47	0.51	0.64
Threshold	2.0	2.4	15	2.3	2.6	20

BrST = breath-hold SPECT; FB = free breathing
AUC = area under the curve, *p < 0.05 (Chi square test)

breathing data in alternate views during the step-and-shoot SPECT cycle. Taking the subject's breath-holding ability into consideration, we set one view to 10 to 15 sec duration. Afterwards, the breath-hold views were extracted and reconstructed to create a breath-hold data set (Fig. 1). The FB views were also reconstructed for comparison.

Data analysis
Quantitative analysis of the abnormal uptake of ^{201}Tl was performed by drawing identical regions of interest (ROIs) over the tumor uptake (T) and contralateral normal lung areas uptake (N) in one transverse section which demonstrated the lesion, including the maximum count, that was selected on both early and delayed images. The mean ROI values (total counts/total pixels) were measured, and the ratios of the tumor uptake to the contralateral normal lung uptake (T/N ratios) were obtained. Below, we refer to the T/N ratio of the early image as the ER and to the T/N ratio of the delayed image as the DR. To quantitatively evaluate the degree of retention in the lesion, the RI was calculated using the following formula: $RI = [(DR - ER)/ER] \times 100$. All patients underwent BrST for ^{201}Tl SPECT.

Then, the SPECT images were compared with chest CT, and accumulation in the lung tumors was evaluated by two nuclear medicine physicians (T.K. and Y.O.).

To compare the diagnostic accuracy of ER, DR, and RI between BrST and FB, ROC analysis was used. To test for differences between these parameters, the Student's t-test and Chi square test were used. The results were considered significant when the p-value was below 0.05.

RESULTS

Table 1 summarizes the results. We examined 10 malignant lesions and 5 benign lesions. The RI of BrST indicated greater accuracy than that of FB in the differential diagnosis of SPN (Tables 2, 3). For the benign lesions, the ER, DR, and RI of BrST were 12.79 ± 1.27, 2.45 ± 0.62, and −3.07 ± 31.51, respectively. The ER, DR, and RI of FB were 2.84 ± 1.35, 2.49 ± 0.84 and, −1.90 ± 37.75, respectively. For the malignant lesions, the ER, DR, and RI of BrST were 2.91 ± 1.62, 3.71 ± 2.11, and 29.86 ± 25.01 ($p < 0.05$), respectively. The ER, DR, and RI of FB were 3.10 ± 1.91 ($p = 0.282$), 3.56 ± 2.48, and 11.52 ± 31.07, respectively.

The RI of BrST was the most useful parameter for differentiating malignant and benign lesions ($p < 0.05$). The sensitivity, specificity, and accuracy in ER were 60, 40, and 53.3%, respectively, for BrST, and 55.6, 60, and 57.1%, respectively, for FB. Those in DR were 70, 60, and 66.7%, respectively, for BrST, and 44.4, 80, 57.1%, respectively, for FB. Those in RI were 80, 80, 80%, respectively, for BrST, and 66.7, 80, 71.4%, respectively, for FB (Table 3). The BrST method improved the diagnostic accuracy for pulmonary lesions.

Case 1
A 75-year-old man complained of hemoptysis. Chest CT scanning showed an abnormal shadow measuring 53 × 39 mm in the right lower lobe (Fig. 2). Both the BrST and FB methods of ^{201}Tl SPECT demonstrated abnormal accumulation (*arrow*) corresponding to the lesion on the delayed images. However, the accumulation in the FB method was divided into two hot nodules (*arrow*). The ER, DR, and RI were 3.00, 4.52, and 50.7, respectively, for the BrST method, and 3.25, 4.25, and 31.2, respectively, for the FB method. This nodule was a non-small cell carcinoma.

Case 2
A 65-year-old man complained of cough. Chest CT scanning showed an abnormal shadow measuring 12 × 10 mm in the right lower lobe (Fig. 3). The BrST method of ^{201}Tl SPECT demonstrated abnormal accumulation corresponding to the lesion on the early images (Fig. 3), whereas the FB method of ^{201}Tl SPECT did not demonstrate any

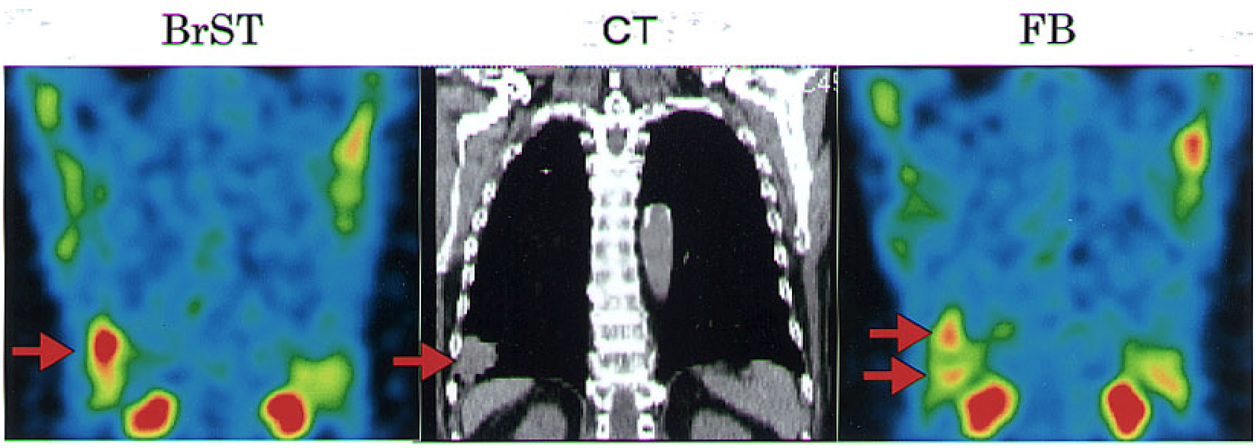

Fig. 2 Case 10. Chest CT scanning showed an abnormal shadow measuring 53 × 39 mm in the right lower lobe. Both of the BrST and FB methods of ^{201}Tl SPECT demonstrated abnormal accumulation (*arrow*) corresponding to the lesion on the delayed images. However, the accumulation in the FB method was divided into two hot nodules (*arrow*). This nodule was a non-small cell carcinoma.

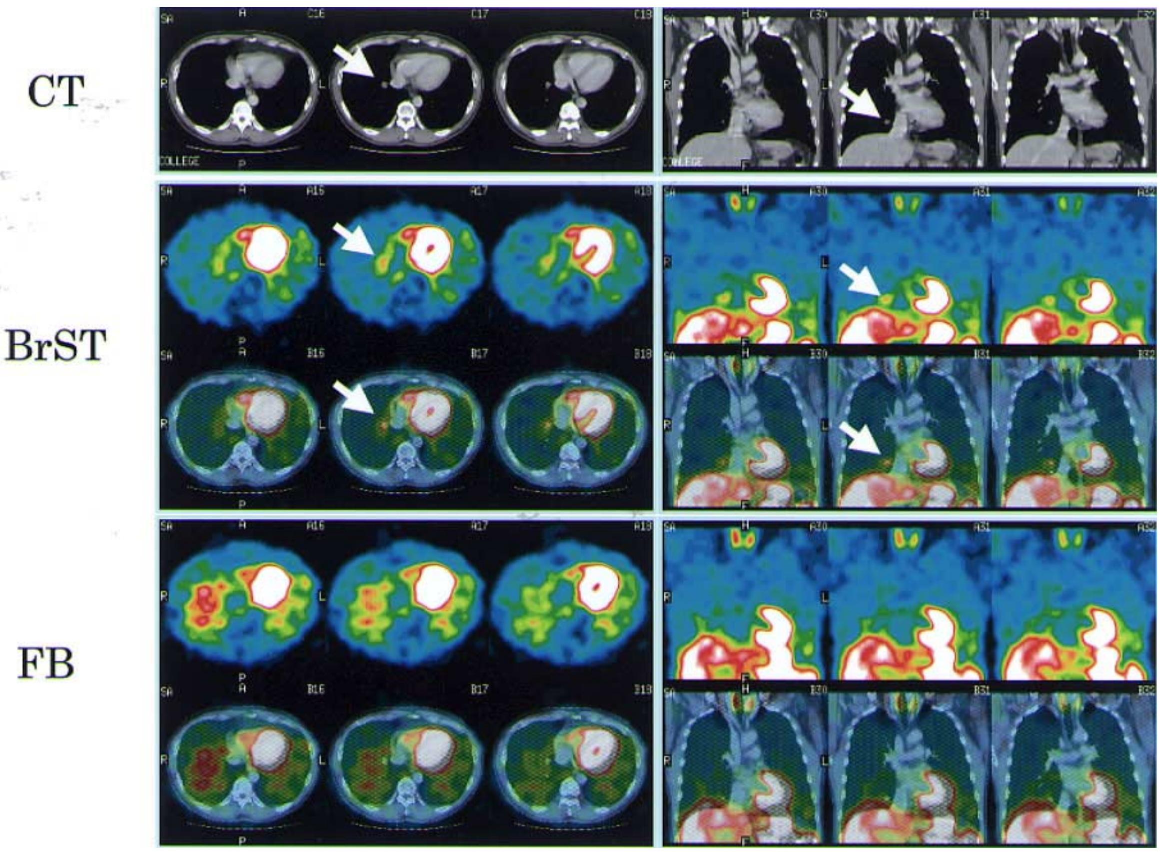

Fig. 3 Case 5. Chest CT scanning showed an abnormal shadow measuring 12 × 10 mm in the right lower lobe. The BrST method of ^{201}Tl SPECT demonstrated abnormal accumulation corresponding to the lesion on the early images, whereas the FB method of ^{201}Tl SPECT did not demonstrate any accumulation. This shadow was a non-small cell lung carcinoma.

accumulation. The ER, DR and RI for the BrST method were 2.11, 2.47, and 17.1, respectively. This shadow was a non-small cell lung carcinoma.

DISCUSSION

It has been reported that ^{201}Tl SPECT is useful for the differentiation between benign and malignant lesions of SPN. The diagnostic ability of ^{201}Tl SPECT has been reported, with sensitivity, specificity, and accuracy of 85 to 100%, 90 to 100%, and 85 to 100%, respectively.[5–7] Higashi et al. reported that the diagnostic accuracy for the pulmonary nodules over 2 cm in size between ^{201}Tl SPECT and FDG-PET is almost the same.

As the BrST method reduces the breathing motion artifacts, its quantitative value is precise and we can evaluate small lesions measuring less than 2 cm.[8,9] We previously demonstrated in experiments using a dynamic phantom, that the normal respiratory SPECT data had respiration-induced motion artifacts, while the breath-hold data did not.[10] Our results showed that the novel BrST method effectively eliminated artifacts induced by the respiratory motion. The use of breath-hold or breath-monitoring methods in the other conventional examinations including CT and MRI is generally known, but there has been no report on the use of the breath-hold method in nuclear medicine examinations. On the other hand, to obtain precise fusion imaging between CT and SPECT images, the breath-monitoring method has been attempted, but this method needs additional chest CT imaging. The BrST method can use the conventional CT images, and therefore does not need additional CT scanning for image registration. The BrST method, consequently, can reduce the costs of medical contamination. To obtain reference SPECT images without breath holding, we used half of the projections recorded during FB. Since breath holding for 15 seconds is a relatively tough task, it is expected that breath holding for 15 seconds may cause hyperventilation during the next 15 seconds, thus increasing the respiratory motion. Therefore, to reduce hyperventilation, the provision of an oxygen supply may be necessary during the examination.

Our results suggest that the differential diagnosis of SPN with ^{201}Tl BrST would become easier than the conventional FB ^{201}Tl method. Our present study focused on only a few cases, and therefore, we have to examine more cases of SPN with ^{201}Tl BrST. FDG-PET is an excellent modality for cancer detection. Nevertheless, it is expensive, its sensitivity is reduced in diabetes mellitus patients, and it is not used widely due to the unavailability of PET. Misregistration of PET/CT may occur when the lesions are near the diaphragm.[11] In contrast, misregistration does not occur in the ^{201}Tl BrST method with CT. Moreover, ^{201}Tl SPECT is used widely and it can be used for diabetic patients.

This novel BrST method showed a greater accuracy than the conventional FB method. The BrST method is applicable to gated-SPECT, static acquisition, and PET-CT, and is therefore a promising technology.

CONCLUSION

We conclude that the retention index of the breath-hold SPECT method is more accurate than that of the conventional free breathing method. The breath-hold SPECT method can evaluate smaller lesions than the free breathing method. This method is applicable to gated-SPECT, static acquisition and PET-CT, and therefore, is thought to be a promising technology.

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