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의학박사 학위논문

Measurement repeatability of
nonsolid nodule in low-dose
lung cancer screening with
monoenergetic images

저선량 폐암 검진에서 단일에너지
영상을 이용한 비고형성 결절의
측정 반복성

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Abstract

Measurement repeatability of nonsolid nodule in low-dose lung cancer screening with monoenergetic images

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Purpose: To investigate whether monoenergetic images captured with dual-layer spectral CT can improve the repeatability of subsolid nodule measurement, and whether this approach can further reduce the radiation dose of computed tomography (CT) while maintaining its measurement repeatability.

Materials and Methods: An anthropomorphic phantom with simulated subsolid nodules at three different levels was repeatedly scanned with both conventional single-energy CT and dual-layer spectral CT. A proxy for the measurement repeatability in the National Lung Screening Trial (proxy for NLST) was calculated with the typical CT protocol used in NLST. Using the dual-layer spectral CT, monoenergetic images of 40 to 110 keV, with an interval of 10 keV, were generated. The average diameter and volume of a

total of 15,660 nodules in 870 CT images were measured by using a commercially-available computer-aided detection system. The repeatability coefficient (RC), %RC, and 95% confidence intervals of each image set were calculated and compared.

Results: At the same tube voltage and tube current-time product, monoenergetic images resulted in significantly lower RC than the proxy for NLST, indicating that measurement repeatability was enhanced. When the radiation dose was lowered by 30% or 55%, monoenergetic images showed significantly lower RC at high-energy keV than the proxy for NLST. The estimated measurement repeatability from monoenergetic images with 30% or 55% lower radiation dose was comparable to the repeatability from conventional single-energy CT images with standard radiation dose and iterative reconstruction.

Conclusion: Monoenergetic images captured by using dual-layer spectral CT can improve the repeatability of subsolid nodule measurement. The use of monoenergetic images would allow lung cancer screening with a lower radiation dose, while maintaining comparable measurement repeatability.

Keywords: Dual-layer spectral CT; lung cancer screening; measurement repeatability; monoenergetic image; radiation dose

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LIST OF ABBREVIATIONS

CAD = Computer-aided detection

CI = Confidence interval

CT = Computed tomography

Lung-RADS = Lung imaging reporting and data system

NCCN = National comprehensive cancer network

NLST = National Lung Screening Trial

RC = Repeatability Coefficient

INTRODUCTION

The National Lung Screening Trial (NLST) showed that the use of low-dose computed tomography (CT) for screening in a high-risk population reduces mortality from lung cancer (1). Lung cancer screening guidelines require a variety of management approaches, according to the size and size changes of the nodules (2, 3). Thus, in addition to nodule detectability, measurement repeatability is an essential factor in screening CT for follow-up and risk assessment of pulmonary nodules. Because annual CT screening increases the risk of radiation-related cancers (4), it is also important to minimize the radiation dose during CT screening. Therefore, it is important for screening to remain effective while reducing the radiation dose; the radiation dose should not be sufficiently low to cause problems in nodule detection or measurement.

It is common to reduce the tube current to reduce the radiation dose in screening CT (5) and the use of the iterative reconstruction technique is known to reduce the radiation dose while maintaining nodule detectability (6). However, small subsolid nodules are not known to exhibit high measurement repeatability in low-dose CT (7). Recent studies, which compared the repeatability of subsolid nodule measurement with iterative reconstruction versus filtered back projection, have shown mixed results regarding whether iterative reconstruction can significantly increase measurement repeatability (7-9).

An important reason for the low repeatability of subsolid nodule measurement in low-dose CT is the presence of beam-hardening artifacts (7). Because monoenergetic images of recently used spectral CTs are effective in reducing the beam-hardening artifacts (10-12), the use of monoenergetic images may increase the measurement repeatability of subsolid nodules in

low-dose CT. Therefore, our phantom study aimed to determine whether monoenergetic images captured with dual-layer spectral CT can improve the repeatability of subsolid nodule measurement and whether this approach can further reduce the radiation dose of CT while maintaining measurement repeatability.

MATERIALS AND METHODS

This study was exempt from Institutional Review Board approval of Seoul National University Bundang Hospital because no animal or human data were acquired.

Anthropomorphic phantom and simulated subsolid nodules

Lung cancer screening CT phantom (LSCT001, Kyoto Kagaku, Japan) is an anthropomorphic phantom dedicated to lung cancer screening conditions. Simulated subsolid nodules are separately embedded in apices, bifurcation, and base of lungs (*Figure 1*). We used three types of nodules in the right lung with 100 HU contrast to the background (12 mm, 10 mm, 8 mm), and three other types of nodules in the left lung with 270 HU contrast to the background (10 mm, 8 mm, 6 mm). Because six subsolid nodules were measured at three different levels, 18 measurements were obtained in one CT scan.

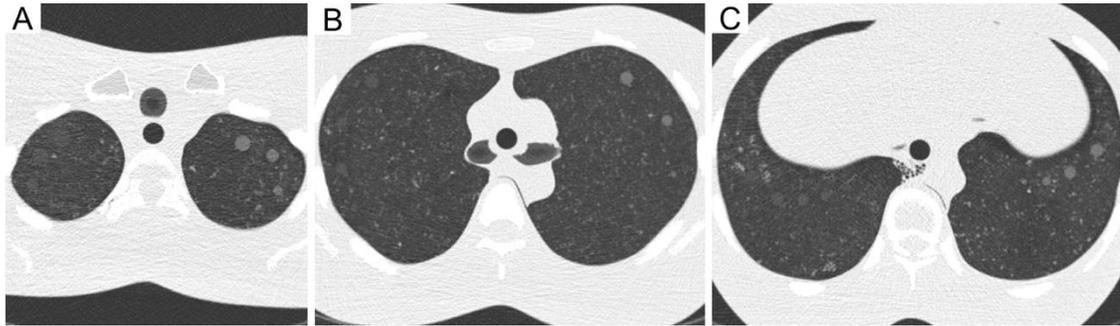


Fig 1. Anthropomorphic phantom with simulated subsolid nodules separately embedded in (A) apices, (B) bifurcation, and (C) base of lungs.

The nodules in the right and left lung have 100 HU and 270 HU contrast to the background, respectively.

Image acquisition

All phantom images were obtained with two 64-row multi-detector CT machines: Brilliance 64, a conventional single-energy CT, and IQon spectral CT (Philips Healthcare, the Netherlands). IQon spectral CT uses a single X-ray tube and dual-layer detectors. The detectors separate the X-ray beam into low-energy (upper layer) and high-energy (lower layer) data, which are used to reconstruct spectral base images. The images contain the raw data of both layers and are used to reconstruct virtual monoenergetic images (13).

All examinations were conducted with a slice thickness of 1 mm and increment of 1 mm, with collimated detector width of 64×0.625 mm. The examinations on Brilliance 64 were performed with 120 kVp tube voltage and two distinct tube current-time products, 30 mAs and 15 mAs. The images on IQon spectral CT were captured with 120 kVp tube voltage and three different tube current-time products: 30 mAs, 15 mAs, and 10 mAs.

Each scan from Brilliance 64 and IQon spectral CT was repeated 30 times under the same conditions for consideration of interscan variation. Each of the images from Brilliance 64 was reconstructed by using two approaches: filtered back projection and iterative reconstruction (iDose⁴ level 5, Philips Healthcare, the Netherlands), as used in our clinical routine. We reconstructed every image taken with IQon spectral CT with a dedicated spectral iterative reconstruction algorithm (Spectral level 5, Philips Healthcare, the Netherlands) developed for the dual-layer spectral detector CT system. Virtual monoenergetic images were reconstructed from 40 keV to 110 keV, with 10-

keV intervals on a workstation with the Spectral CT Viewer (Spectral Diagnostics Suite, Philips Healthcare, the Netherlands) (11). Also, to confirm the effect of monoenergetic images within the same CT machine, 30 polychromatic CT images were generated at 120 kVp and 30 mAs with dual-layer spectral CT using iterative reconstruction.

Estimated radiation doses expressed in CTDI_{vol} for all CT protocols are tabulated in *Table 1*. To calculate a proxy for the measurement repeatability in NLST (hereinafter referred to as the proxy for NLST), we used CT images that were taken at the typical NLST setting of 120 kVp tube voltage and 30 mAs tube current-time product, then reconstructed with filtered back projection (14).

Table 1. Estimated radiation dose for CT protocols

	Tube voltage (kVp)	Tube current-time products (mAs)	CTDI _{vol} (mGy)	Radiation dose compared to typical NLST scan	Radiation dose compared to proxy for NLST
IQon	120	30	2.7	93%	135%
		15	1.4	48%	70%
		10	0.9	31%	45%
Brilliance 64	120	30	2.0	69%	100%
		15	1.0	34%	50%

CTDI, computed tomography dose index; NLST, National Lung Screening Trial.

Measurements

The reconstructed images were evaluated on a workstation using a commercially available computer-aided detection (CAD) system for CT examinations (Intellispace Portal v8, Lung Nodule Assessment, Philips Healthcare, the Netherlands). The CAD system provides quantitative information about the size of lung nodules via volume segmentation (15). It automatically performs lesion segmentation after a user clicks on the pulmonary nodules (*Figure 2*). No manual correction was performed, except to click again when the CAD system failed on lesion segmentation. The CAD system calculated the average diameter and the volume of each lesion, according to the lesion segmentation. The average diameter is the mean of the longest diameter of the nodule and its perpendicular diameter and has been adopted in lung cancer screening guidelines (2, 3).

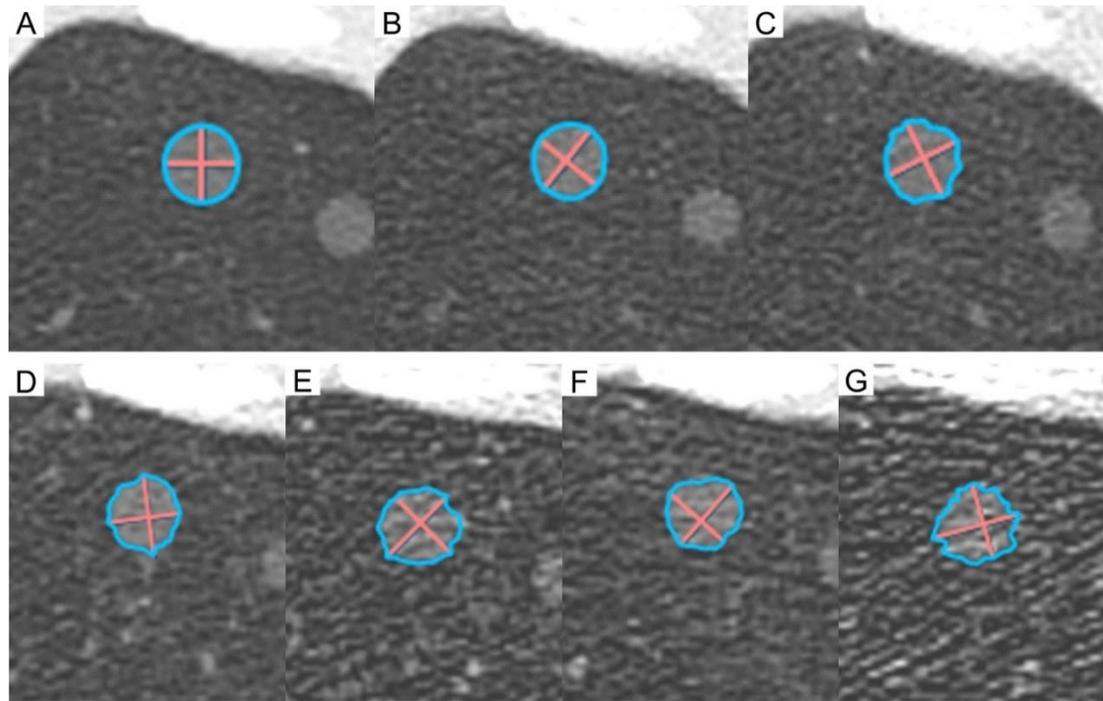


Fig 2. Automatic nodule segmentation using a computer-aided detection system for a 10 mm subsolid nodule captured with dual-layer spectral CT (A–C) and conventional single-energy CT (D–G). Tube current-time products and reconstruction methods of each CT protocol: (A) 30 mAs, 100 keV monoenergetic image; (B) 15 mAs, 100 keV monoenergetic image; (C) 10 mAs, 100 keV monoenergetic image; (D) 30 mAs, iterative reconstruction; (E) 30 mAs, filtered back projection; (F) 15 mAs, iterative reconstruction; and (G) 15 mAs, filtered back projection.

Statistical analysis

To calculate the measurement precision of the subsolid nodules of various sizes and densities, the repeatability coefficient (RC), which solely reflects within-subject variance, was used as recommended by the Quantitative Imaging Biomarkers Alliance metrology group (16, 17). The RC was presented with 95% confidence interval (CI); %RC was tabulated in the table for intuitive comprehension of measurement precision. Lower values of RC or %RC indicate better repeatability. We defined a statistically significant difference in measurement precision between the two techniques when the 95% CI ranges did not overlap. Statistical analysis was performed by using commercially available software (Excel 2016, Microsoft, USA; Prism 7, GraphPad Software, USA).

RESULTS

With the conventional single-energy CT, 30 images were taken with each of the two tube current-time products (30 mAs and 15 mAs) at 120 kVp tube voltage. Those images were then reconstructed by two methods of filtered back projection and iterative reconstruction (iDose⁴ level 5). Therefore, 120 CT images were generated with the conventional single-energy CT. Additionally, 30 images were taken with IQon spectral CT at the same tube voltage of 120 kVp and each of three different tube current-time products (30 mAs, 15 mAs, and 10 mAs). A total of 720 CT images were generated because we reconstructed each of the images into eight monoenergetic images at 10-keV intervals from 40 to 110 keV. Also, to confirm the effect of monoenergetic images within the same CT machine, 30 polychromatic CT images were generated at 120 kVp and 30 mAs with dual-layer spectral CT using iterative reconstruction. With those 870 CT images, the average diameter and volume of six types of nodules were measured at three different levels of apices, bifurcation, and base of lungs. Therefore, measurement data were produced and analyzed for 15,660 nodules. The RC and %RC values for the average diameter and volume, on the basis of CT protocol and reconstruction method, are presented in *Figure 3* and *Table 2*, respectively.

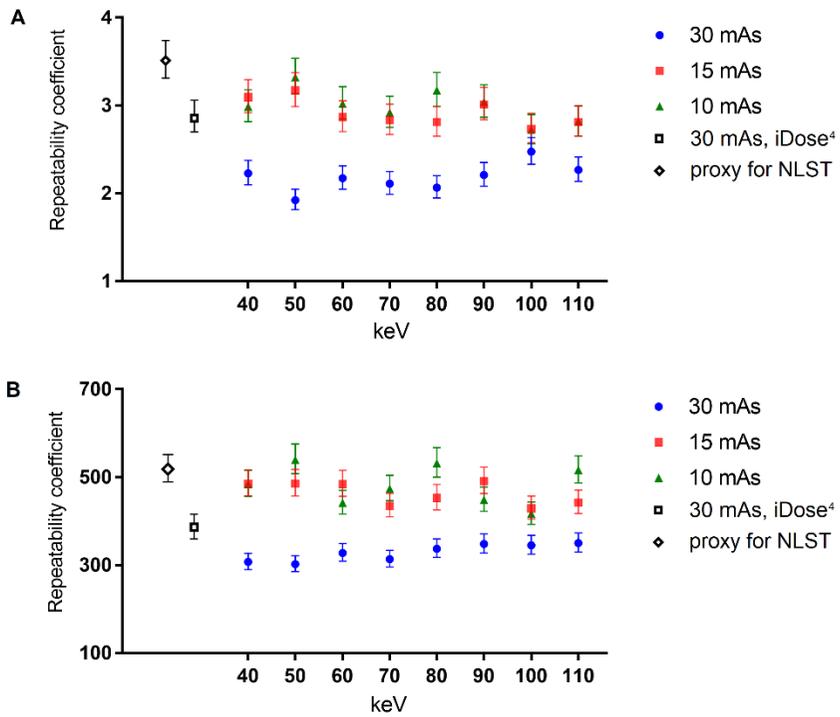


Fig 3. Repeatability coefficients of (A) average diameter and (B) volume measurements of monoenergetic images reconstructed with different energy levels, compared with the conventional image with iterative reconstruction from dual-layer spectral CT and the proxy for the measurement repeatability in NLST (proxy for NLST). Point estimates of repeatability coefficient are presented with 95% confidence intervals. NLST, National Lung Screening Trial.

Table 2 Repeatability coefficient for subsolid nodule measurement across different tube current-time products and reconstruction methods

Tube current-time products (mAs)	Reconstruction methods	Average diameter	Volume
30	FBP	36.4 (34.32–38.75)	117.83 (111.10–125.44)
	iDose ⁴	31.97 (30.14–34.03)*	104.76 (98.78–111.53)
15	FBP	38.84 (36.62–41.35)	137.84 (129.96–146.74)**
	iDose ⁴	33.76 (31.83–35.94)	112.69 (106.25–119.97)
30 (IQon)	iDose ⁴	29.97 (28.26–31.91)*	77.24 (72.82–82.22)*
	40 keV	23.93 (22.56–25.47)*	63.03 (59.43–67.10)*
	50 keV	20.13 (18.98–21.43)*	61.39 (57.88–65.35)*
	60 keV	22.71 (21.41–24.17)*	68.06 (64.17–72.46)*
	70 keV	22.12 (20.86–23.55)*	64.82 (61.12–69.01)*
	80 keV	21.64 (20.41–23.04)*	70.93 (66.88–75.51)*
	90 keV	23.12 (21.80–24.61)*	73.25 (69.07–77.99)*
	100 keV	25.75 (24.28–27.41)*	71.54 (67.45–76.16)*
15 (IQon)	110 keV	23.81 (22.45–25.35)*	74.7 (70.43–79.53)*
	40 keV	32.45 (30.59–34.54)	105.73 (99.69–112.56)
	50 keV	33.24 (31.34–35.38)	108.96 (102.74–116)
	60 keV	30.12 (28.40–32.06)*	104.72 (98.74–111.49)
	70 keV	29.82 (28.12–31.75)*	95.02 (89.59–101.15)*
	80 keV	29.31 (27.64–31.21)*	102.84 (96.96–109.48)*
	90 keV	31.88 (30.06–33.94)*	108.38 (102.18–115.38)
10 (IQon)	100 keV	28.81 (27.17–30.67)*	95.05 (89.62–101.19)*
	110 keV	29.54 (27.85–31.45)*	96.65 (91.12–102.89)*
	40 keV	31.69 (29.88–33.74)*	109.69 (103.42–116.77)
	50 keV	34.83 (32.84–37.08)	122.02 (115.04–129.9)
	60 keV	31.94 (30.11–34)*	101.61 (95.81–108.18)*
	70 keV	31.11 (29.33–33.12)*	111.25 (104.89–118.44)
	80 keV	33.59 (31.67–35.76)	126.57 (119.34–134.75)
	90 keV	32.46 (30.60–34.55)	106.14 (100.07–112.99)
	100 keV	28.94 (27.29–30.81)*	98.35 (92.73–104.70)*
	110 keV	29.89 (28.18–31.82)*	118.31 (111.55–125.95)

Results are presented as %RC and 95% confidence interval in parentheses. *, significantly better than the proxy for NLST; **, significantly worse than the proxy for NLST; RC, repeatability coefficient.

The monoenergetic images taken by IQon spectral CT showed improved measurement repeatability compared with the images taken by the conventional single-energy CT with 120 kVp tube voltage, 30 mAs tube current-time product, and filtered back projection, which is a proxy for NLST. The RC for the average diameter and volume measurement in every set of eight monoenergetic images with 120 kVp tube voltage and 30 mAs tube current-time product was significantly lower than the proxy for NLST. The monoenergetic images with 15 mAs tube current-time product, which reduced the radiation dose by 30% relative to the proxy for NLST, also showed a lower point estimate of RC relative to the proxy for NLST. In the monoenergetic images with 10 mAs tube current-time product, the results were identical with the exception of the volume measurements at 50, 80, and 110 keV. The repeatability significantly improved in both average diameter and volume measurements in monoenergetic images of 70 keV, 80 keV, 100 keV, and 110 keV with 15 mAs tube current-time product, as well as 60 keV and 100 keV with 10 mAs tube current-time product. The repeatability of average diameter measurement was significantly improved more frequently with the monoenergetic images of reduced radiation dose (15 mAs and 10 mAs tube current-time product), than the repeatability of volume measurement (*Figure 3*).

Table 2 shows the %RCs derived from multiple measurements of the average diameter and volume of subsolid nodules. The RC of measurements in the images of the 120 kVp tube voltage and 30 mAs tube current-time product obtained by conventional single-energy CT was lower with iterative

reconstruction (iDose⁴ level 5) than the RC with filtered back projection. The RC of average diameter measurement significantly improved. However, monoenergetic images taken from the same 30 mAs tube current-time product resulted in significantly lower RC than the images with iterative reconstruction. Additionally, the high energy level (60 keV or higher) monoenergetic images with reduced radiation dose of 15 mAs tube current-time product yielded a lower point estimate of RC, compared with the images with 30 mAs tube current-time product and iterative reconstruction. The RC calculated from monoenergetic images with 10 mAs tube current-time product showed mixed results when compared with the RC from the conventional single-energy CT images with iterative reconstruction. In conventional single-energy CT, when the radiation dose was reduced by using the 15 mAs tube current-time product, the RC increased relative to the proxy for NLST. However, when iterative reconstruction was applied to the images with 15 mAs tube current-time product, measurement repeatability was comparable to that of the proxy for NLST. Of note, 100 keV monoenergetic images with 10 mAs tube current-time product showed significantly better repeatability in both average diameter and volume measurements than the images with 15 mAs tube current-time product and iterative reconstruction.

DISCUSSION

Our study's aim was to determine whether the repeatability of subsolid nodule measurement can be controlled by using virtual monoenergetic images. In the lung cancer screening guidelines, such as lung-RADS and NCCN guideline, the average diameter is used as the size criterion for nodule follow-up and management (2, 3); in the Dutch-Belgian NELSON trial, the volume was used as a similar criterion (18). Naturally, the determination of nodule follow-up and management in lung cancer screening are not based on the actual size of the nodules in surgical specimens, but on the size measured on CT and changes in size over time. Therefore, rather than focusing on the measurement accuracy of how closely the actual nodule size is measured, our study focused on the measurement precision of subsolid nodules, showing how average diameter and volume on low-dose CT were measured consistently to determine their sizes and changes.

We used calculated RC from 30 CT images from a conventional single-energy CT with a scan protocol of 120 kVp tube voltage, 30 mAs tube current-time product and filtered back projection, as a proxy for measurement repeatability in NLST. It is reasonable to assume that the measurement repeatability calculated from our proxy for NLST, which used a 64 detector-row CT machine with typical NLST protocol, is not inferior to the mean measurement repeatability of actual NLST protocols, which typically used 4 to 16-channel CT machines (14). Therefore, our results conservatively reflect the degree to which the monoenergetic image enhances measurement

repeatability.

Our study results show that monoenergetic images increase repeatability in measurement of the average diameter and volume of subsolid nodules. When compared with the proxy for NLST, the use of monoenergetic images with reduced radiation dose (tube current-time product of 50% or 33%) lowered the point estimate of the RC, which indicated that measurement repeatability was improved, even with lower radiation risks. In monoenergetic images with tube current-time product of 15 mAs, the calculated RCs of 70 keV, 80 keV, 100 keV, and 110 keV were significantly lower than the RC of the proxy for NLST, both in average diameter and volume measurement. In contrast, the RC of the volume measurement was significantly worse when the tube current-time product was reduced to 15 mAs in the conventional single-energy CT. When compared with conventional single-energy CT images using 30 mAs and iterative reconstruction (iDose⁴ level 5), the point estimates of RC calculated from monoenergetic images of high energy level (60 keV or higher) were lower, even with reduced radiation dose.

Recent studies showed that monoenergetic images may improve the image quality not only by reducing beam-hardening artifacts, but also by increasing contrast-to-noise ratio (19) and reducing photon starvation artifacts (20). Even when the tube current-time product was reduced to 10 mAs, the RC of high energy level (100 keV) monoenergetic images was significantly lower than the RC of the proxy for NLST and the RC of the images with 15 mAs tube current-time product and iterative reconstruction. The significant improvements in measurement repeatability at lower radiation doses can be

attributed to the reduction of beam-hardening artifacts and photon starvation artifacts.

As we measured small subsolid nodules, the %RC of volume measurement in our study was higher than that of another recent article assessing the volumetric measurement of synthetic nodules (7). This may be because of differences in the CAD system itself, or the fact that our measurement methods do not incorporate manual correction after clicking on the nodule in the CAD system. The section thickness of the CT images used in that article was 0.5 mm; whereas it was 1.0 mm in the present study. However, we believe our results are credible because we compared the RCs calculated from monoenergetic images with the proxy for NLST, which was obtained from images taken with a clinically validated CT protocol. The monoenergetic images and images with typical NLST protocol were generated and investigated in the same manner in our study. We minimized the possibility of manual intervention of investigators in our measurement methods and included a greater pool of measurement data in our study. It is understandable that the precision of volume measurement is lower for small subsolid nodules in CT images taken with a low-dose protocol when compared with an article investigating measurement reproducibility of solid pulmonary nodules (21),

Our study has limitations. First, we calculated RC with CT images of simulated subsolid nodules in an anthropomorphic phantom, rather than actual CT images of human subjects. Additional validation studies with respect to target populations may be required to apply our results to lung cancer screening. Second, although the measurement repeatability of conventional

polychromatic images with iterative reconstruction was inferior to the repeatability of monoenergetic images at the same dose level, it is difficult to verify the effect of different CT systems on measurement repeatability in our study. While a recent study showed that conventional single-energy CT and dual-layer spectral CT resulted in similar image quality at equivalent dose levels (22), it is not clear whether the measurement repeatability is affected by different CT systems. However, the main purpose of our study is to determine whether monoenergetic images taken with dual-layer spectral CT have advantages over the proxy for clinically validated NLST protocol and we believe that the results of our study are in line with the purpose. Third, our study did not investigate how the measurement repeatability of the nodule is affected by the size, density, shape, or location of the nodule. However, our study design reflects our consideration of the general performance and radiation dose of the CT protocol in the detection and measurement of various lesions in a real clinical setting; notably, it does not reflect consideration of the properties of individual nodules when choosing a CT protocol for lung cancer screening. Fourth, as we conducted our CT scan repeatedly without physical movement of the phantom nodules or significant time interval, the measurement repeatability in real clinical practice could be affected by those other physical factors which our study design might have overlooked. Also, as nodule measurement with CAD system does not necessarily produce a uniform result between repeated attempts, the measurement repeatability could be affected by the operator of the CAD system. We tried to minimize those effects by carefully giving measurement seeds at the very center of each

simulated nodules in our study. Lastly, it is not clear whether variability for subsolid nodule classification might be affected on monoenergetic images. Recent studies showed that the observer variability for subsolid nodule classification is considerable (23, 24). Although another recent study showed that nodule classification exhibits interchangeability between low-dose and standard-dose chest CTs (25), further investigation is needed regarding the variability of subsolid nodule classification in monoenergetic images with lower radiation dose, as used in our study.

CONCLUSIONS

Our phantom study shows that monoenergetic images captured by using dual-layer spectral CT can improve the measurement repeatability of subsolid nodules. Therefore, the use of monoenergetic images might allow lung cancer screening with a lower radiation dose while maintaining comparable measurement repeatability.

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국문 초록

목적: 이중층 스펙트럼 CT(computed tomography)로 촬영된 단일에너지 영상이 비고형성 결절 측정의 반복성을 향상시킬 수 있는지, 그리고 이 영상 기법이 측정 반복성을 유지하면서 CT 의 방사선량을 추가로 감소시킬 수 있는지 여부를 조사하고자 함.

방법: 세 가지 다른 위치에 가상 비고형성 결절들을 포함하고 있는 인체 모형 팬텀을 기존의 단일에너지 CT 와 이중층 스펙트럼 CT 를 이용하여 반복적으로 촬영하였다. National Lung Screening Trial (NLST) 에서의 측정 반복성에 대한 대리 표지자는 NLST 에서 일반적으로 사용된 조건들을 사용하여 단일 에너지 CT 로 촬영하여 계산하였다. 이중층 스펙트럼 CT 를 사용하여 10 keV 의 간격으로 40 keV 에서 110 keV 의 다양한 단일에너지 영상이 생성되었다. 이렇게 생성된 870 개의 CT 영상에서 총 15,660 개의 결절의 평균 직경과 부피를 시판되는 컴퓨터 보조 검출 시스템을 사용하여 측정하였다. 각각의 영상에 대한 반복계수와 백분율로 표시된 반복계수, 그리고 95 % 신뢰구간을 계산하고 비교했습니다.

결과: 동일한 관전압 및 관전류에서 촬영했을 때 단일 에너지 이미지는 NLST 의 대리 표지자보다 훨씬 낮은 반복계수를 나타내어 측정 반복성이 향상되었음을 나타냈다. 방사선량이 30 % 또는 55 % 감소되었을 때에도 고에너지 keV 하에서의 단일 에너지 영상은 NLST 의 대리 표지자보다 낮은 반복계수를 보였다. 30 % 또는 55 % 더 낮은 방사선량을 보인 단일 에너지 영상으로부터 계산된 측정 반복성은, 표준 방사선량으로 촬영하여 반복영상재구성 기법으로 재구성한 기존의 단일 에너지 CT 이미지의 반복성에 필적했다.

결론: 이중층 스펙트럼 CT 에서 촬영하고 재구성된 단일에너지 영상은 비고형성 결절 측정의 반복성을 향상시킨다. 또한 단일에너지 영상을 사용하면 측정 반복성을 유지하면서 방사선량을 낮추어 폐암 선별 검사를 시행할 수 있게 된다.

주요어 : 이중층 스펙트럼 CT, 폐암검진, 측정 반복성, 단일에너지 영상, 방사선량

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