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FULL PAPER

Accuracy of lung nodule volumetry in low-dose CT with iterative reconstruction: an anthropomorphic thoracic phantom study

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Objective: The purpose of this study was to assess accuracy of lung nodule volumetry in low-dose CT with application of iterative reconstruction (IR) according to nodule size, nodule density and CT tube currents, using artificial lung nodules within an anthropomorphic thoracic phantom.

Methods: Eight artificial nodules (four diameters: 5, 8, 10 and 12 mm; two CT densities: -630 HU that represents ground-glass nodule and +100 HU that represents solid nodule) were randomly placed inside a thoracic phantom. Scans were performed with tube current-time product to 10, 20, 30 and 50 mAs. Images were reconstructed with IR and filtered back projection (FBP). We compared volume estimates to a reference standard and calculated the absolute percentage error (APE).

Results: The APE of all nodules was significantly lower when IR was used than with FBP ($7.5 \pm 4.7\%$ compared with $9.0 \pm 6.9\%$; $p < 0.001$). The effect of IR was more pronounced for smaller nodules ($p < 0.001$). IR showed a

significantly lower APE than FBP in ground-glass nodules ($p < 0.0001$), and the difference was more pronounced at the lowest tube current ($11.8 \pm 5.9\%$ compared with $21.3 \pm 6.1\%$; $p < 0.0001$). The effect of IR was most pronounced for ground-glass nodules in the lowest CT tube current.

Conclusion: Lung nodule volumetry in low-dose CT by application of IR showed reliable accuracy in a phantom study. Lung nodule volumetry can be reliably applicable to all lung nodules including small, ground-glass nodules even in ultra-low-dose CT with application of IR.

Advances in knowledge: IR significantly improved the accuracy of lung nodule volumetry compared with FBP particularly for ground-glass (-630 HU) nodules. Volumetry in low-dose CT can be utilized in patient with lung nodule work-up, and IR has benefit for small, ground-glass lung nodules in low-dose CT.

The volumetric measurement of a lung nodule with CT imaging is more accurate and consistent in the detection of growth and determination of tumour doubling time than simple manual axial diameter measurements used in the New Response Evaluation Criteria in Solid Tumours (revised RECIST guideline v. 1.1).^{1,2} The recent Dutch-Belgian randomized lung cancer screening trial (NELSON) nodule management protocol was based on volumetric nodule assessment. A test was considered to be positive if the solid component of a nodule measured $>500 \text{ mm}^3$, or if the solid component of a nodule was $50\text{--}500 \text{ mm}^3$ when the volume doubling time was less than 400 days.³ Therefore, pulmonary nodule volumetry is used for nodule identification and diagnostic strategy guidance in the follow-up of lung cancer screening as well as for monitoring tumour response to therapy.

The increase in the use of CT has raised concern about the increasing risk of cancer from medical radiation exposure.⁴ Thoracic CT has been widely used in variable disease entities and frequent follow-up CT examinations may be needed. Additionally, lung cancer screening using CT is becoming more common. Therefore, further reduction of the radiation exposure during chest CT examinations would be required, and radiation dose reduction is very important issue in lung cancer screening and in lung nodule work-up. For lowering the radiation dose, the use of iterative reconstruction (IR) algorithms has become available, due to advances in technology and increased computational power. IR provides imaging at lower radiation doses with similar noise levels compared with routine-dose conventional filtered back projection (FBP), allowing dose reduction without compromising on image quality and diagnostic value.⁵⁻¹⁰ Among the several IR

algorithms offered by different vendors, we used adaptive iterative dose reduction system using a three-dimensional processing algorithm (AIDR 3D; Toshiba Medical Systems, Otawara, Japan).

The accuracy of volumetric measurements of lung nodules can be affected by many sources of variability, such as nodule characteristics, CT scan parameters and measurement technology.^{11–15} Several studies have examined the accuracy of volumetric measurement of lung nodules in low-dose CT.^{16–18} However, it is still not well known whether IR algorithm can be a source of variability in nodule volume measurement. Furthermore, the effect of lower dose CT on volumetric measurement in relation to nodule density and image reconstruction algorithm has not been investigated.

The purpose of this study was to assess the accuracy of lung nodule volumetry in low-dose CT using IR according to different nodule sizes, nodule densities, CT tube currents and scan types using spherical synthetic pulmonary nodules inside an anthropomorphic thoracic phantom.

METHODS AND MATERIALS

Anthropomorphic thoracic phantom and synthetic lung nodules

A commercially available anthropomorphic thoracic phantom (Chest Phantom N1; Kyoto Kagaku Co., Ltd, Kyoto, Japan) was used. The phantom consists of a life-size anatomical model of a

male thorax with soft-tissue substitute materials made of polyurethane resin composites and synthetic bones made of epoxy resin, all with X-ray absorption rates very close to those of the corresponding human tissues. Three-dimensional pulmonary vessels and bronchi up to the first bifurcation are arranged in the phantom lung.

We used eight spherical synthetic pulmonary nodules (Chest Phantom N1) with four diameters (5, 8, 10 and 12 mm, corresponding to a volume of 65.4, 267.9, 523.3 and 904.3 mm³, respectively) and 2 densities (−630 and +100 HU), which represent the range in densities expected in clinical imaging. The −630 HU spheres, made of polyurethane foam resin, represented ground-glass nodules, and the +100 HU spheres, made of polyurethane resin, represented solid nodules (Figure 1). The simulated nodules were randomly inserted into the phantom using double-sided tape. None of the nodules was attached to pleura or located subpleurally.

CT imaging parameters

Scanning was performed using a 320-row CT scanner (Aquilion™ ONE; Toshiba Medical Systems, Otawara, Japan). The CT examination for each imaging protocol was repeated five times. Image acquisition was performed using tube current settings of 10, 20, 30 and 50 mAs, which represent low-dose and ultra-low-dose CT scans. The scan protocol included two scanning mode patterns: 80-detector row helical scans and 320-detector

Figure 1. (a) An anthropomorphic thoracic phantom and (b) artificial pulmonary nodules with four diameters (5, 8, 10 and 12 mm, corresponding to volumes of 65.4, 267.9, 523.3 and 904.3 mm³) and two densities [+100 (top) and −630 HU (bottom)].

Figure 2. Representative images of a nodule with -630 HU density and 8-mm diameter (arrows), acquired at 120 kVp and 10 mAs: (a) on axial CT scan obtained using helical scan and iterative reconstruction (IR), the absolute percentage error (APE) was 22.6. (b) Using helical scan and filtered back projection (FBP), the APE was 30.2. (c) Using volume scan and IR, APE was 19.2. (d) Using volume scan and FBP, APE was 26.4. APE was significantly lower when IR was used ($p < 0.0001$) in ground-glass nodules.

row volume scans. Other scan parameters were the same for each CT protocol: peak tube voltage, 120 kV; collimation, 0.5 mm; gantry rotation time, 500 ms; and pitch value, 1.0. Scans were reconstructed with a slice thickness of 0.5 mm, an increment of 0.5 mm and a field-of-view of 350 mm. We reconstructed all CT images with both IR and FBP. Among the several IR algorithms offered by different vendors, AIDR 3D by Toshiba Medical Systems was used.

All data sets were reconstructed by using standard reconstruction kernel (FC05), which is commonly used for lung imaging in our hospital. In total, 640 nodule measurements were acquired [$5 \text{ repeats} \times 4 \text{ nodule sizes} \times 2 \text{ nodule densities} \times 4 \text{ tube current-time settings} \times 2 \text{ scan types (helical and volumetric)} \times 2 \text{ reconstruction algorithm methods}$] and compared with the true volumes. Examples of scans of a ground-glass nodule with 8-mm diameter acquired at 10 mAs are shown in Figure 2.

Volume measurement method

All data sets were transferred to workstations using commercially available semi-automatic software (Vitrea® advanced v. 6.2; Vital Images, Minnetonka, MN). Nodule segmentation was performed by clicking in the centre of a nodule by one radiologist, and starting automated delineation and quantification. The nodule segmentation algorithm is an intensity-/density-based algorithm that uses tissue density (Hounsfield unit) to separate nodules from background tissues.¹⁹ The algorithm segmented the nodule, calculated its volume and presented the result. In order to minimize observer influence, only these automated

results were used for this study, and no manual correction of lesion margins was performed.

Analysis of nodule volumes and statistics

The volume measurements were used to calculate the absolute percentage error (APE), which was calculated as follows: $100 \times |V_m - V_{rs}| / V_{rs}$, where V_m is the measured nodule volume and V_{rs} is the corresponding reference standard nodule volume. APE was expressed as mean $\pm$ standard deviation. The mean difference between APEs was calculated as APE with FBP – APE with IR, where the APE with IR is measured on images reconstructed with IR, and the APE with FBP is measured on images reconstructed with FBP.

A linear mixed model was fitted to the repeated measures of volume data to estimate the effect of nodule characteristics and CT scan parameters on difference of volumetric error between IR and FBP. The Tukey–Kramer *post hoc* test was used for compensation for multiple comparison. A linear mixed model with Tukey–Kramer *post hoc* comparisons was utilized to identify which factors contributed significantly to the mean difference between APEs as an individual variable, or as part of a significant interaction between variables. The factors included nodule size, nodule density, CT tube current and scan type. The analysis included hypothesis testing using F statistics to determine whether each variable or interaction contributed significantly to the mean difference between APEs. Paired t -test and Wilcoxon signed rank test were used to compare the mean APE between the image reconstruction protocols. Statistical analysis

was performed by using SPSS® v. 20.0 (SPSS Inc, Chicago, IL) and SAS v. 9.2 (SAS Institute, Cary, NC). $p < 0.05$ was taken to be significant.

RESULTS

Measured nodule volumes and volumetric error with IR and FBP reconstruction and various CT tube currents are listed in Table 1. APE across all nodules was significantly lower when IR was used ($n = 320$), with an APE of $7.5 \pm 4.7\%$, than $9.0 \pm 6.9\%$ for FBP ($n = 320$) ($p < 0.001$).

Effects of nodule characteristics and CT parameters on nodule volumetry

Nodule size, nodule density, CT tube current and scan type all contributed significantly to the mean difference of APE. On the basis of F ratio, the nodule density was the most significant individual factor, followed by CT tube current, nodule size and scan type. The results showed significant interactions between nodule size and CT tube current, and nodule density and CT tube current, as paired variables ($p < 0.0001$). Other significant cross-effects were nodule density and scan type, nodule size and nodule density and nodule size and scan type. The most significant interaction was nodule density with CT tube current (Table 2).

Effects of iterative reconstruction on nodule volumetry

The APE of the nodules ≤ 8 mm was larger than that of the nodules ≥ 10 mm. APE with IR was significantly lower than the APE with FBP, in 5 mm ($p < 0.001$) and 12 mm ($p = 0.01$) for both solid and ground-glass nodules (Table 3). The mean difference of APEs was significantly different between the nodules measuring 5 mm and those measuring 8, 10 and 12 mm and between the 8-mm and 10-mm nodules ($p < 0.0001$) (Figure 3a,b).

Effects of iterative reconstruction on nodule volumetry was more pronounced for ground-glass nodules

The APE with IR and the APE with FBP of solid nodules were $4.5 \pm 2.0\%$ and $3.9 \pm 2.0\%$, which were lower than those of ground-glass nodules ($10.5 \pm 4.8\%$ and $14.1 \pm 6.3\%$). For the ground-glass nodules, the APE was significantly lower when IR was used ($p < 0.0001$). In the case of the solid nodules, the APE was significantly lower when FBP was used (Table 3). The mean differences of APEs were significantly different between those of ground-glass and those of solid nodules, implying a greater effect of IR for ground-glass nodule measurement accuracy (Figure 4a,b).

Effects of iterative reconstruction on nodule volumetry was more pronounced for lower CT tube current

The APE with FBP at a tube current of 10 mAs was >20 , >30 and >50 mAs. Although the APE with IR at tube current 10 mAs was >20 , >30 and >50 mAs, it remained within 10%. The APE with IR was significantly lower than the APE with FBP at tube current 10 and 20 mAs ($p < 0.005$). In the case of higher CT tube current (30 and 50 mAs), there was no significant difference between APEs with IR and FBP (Table 4). The mean differences of APEs were significant between all paired dose settings. The effect was more pronounced for the lower tube current, for which the APE was $8.1 \pm 5.7\%$ for IR and $12.6 \pm 9.9\%$ for FBP at a tube current of 10 mAs ($p < 0.0001$) (Figure 5a,b). Especially for ground-glass nodules, the APE with FBP increased as tube current decreased, and the APE with FBP was $21.3 \pm 6.1\%$ at a tube current of 10 mAs. However, the APE with IR at a tube current of 10 mAs was $11.8 \pm 5.9\%$ ($p < 0.0001$) (Table 4).

Table 1. Measured nodule volume and error by different nodule sizes, nodule densities, CT tube currents and reconstruction algorithms

Nodule characteristics	Type of artificial nodules							
	+100 HU density				−630 HU density			
	5 mm diameter	8 mm diameter	10 mm diameter	12 mm diameter	5 mm diameter	8 mm diameter	10 mm diameter	12 mm diameter
Reference standard volume (mm ³)	65.4	267.9	523.3	904.3	65.4	267.9	523.3	904.3
Mean volume in mm ³ (percentage error)								
10 mAs, IR	69.7 (6.5)	276.7 (3.3)	546.8 (4.5)	931.9 (3.1)	61.9 (−5.3)	213.6 (−20.3)	468.6 (−10.5)	804.4 (−11.1)
10 mAs, FBP	69.7 (6.6)	274.0 (2.3)	542.7 (3.7)	927.4 (2.6)	50.1 (−23.4)	198.5 (−25.9)	437.8 (−16.3)	725.7 (−19.8)
20 mAs, IR	69.5 (6.3)	274.9 (2.6)	546.8 (4.5)	930.3 (2.9)	63.2 (−3.3)	220.0 (−17.9)	477.5 (−8.8)	818.6 (−9.5)
20 mAs, FBP	69.6 (6.4)	273.3 (2.0)	543.1 (3.8)	925.5 (2.3)	57.6 (−11.9)	217.6 (−18.8)	469.9 (−10.2)	798.1 (−11.8)
30 mAs, IR	71.4 (9.1)	277.9 (3.7)	545.2 (4.2)	933.6 (3.2)	58.1 (−11.2)	224.0 (−16.4)	482.2 (−7.9)	835.4 (−7.6)
30 mAs, FBP	70.6 (7.9)	275.2 (2.7)	543.6 (3.9)	930.8 (2.9)	56.7 (−13.4)	224.3 (−16.3)	480.0 (−8.3)	828.2 (−8.4)
50 mAs, IR	70.0 (7.0)	277.4 (3.6)	543.6 (3.9)	933.8 (3.3)	59.6 (−8.9)	229.5 (−14.3)	486.2 (−7.1)	843.8 (−6.7)
50 mAs, FBP	69.3 (6.0)	276.1 (3.1)	542.9 (3.8)	931.0 (3.0)	58.3 (−10.9)	227.1 (−15.3)	485.7 (−7.2)	838.0 (−7.4)

FBP, filtered back projection; IR, iterative reconstruction.

Table 2. Effects of nodule characteristics and CT parameters on the mean difference between absolute percentage errors (APEs)

Effect	F-value	p-value
Size	154.22	<0.0001
Density	567.09	<0.0001
CT tube current	312.64	<0.0001
Scan type	12.65	0.0005
CT tube current × nodule size	34.95	<0.0001
CT tube current × nodule density	252.22	<0.0001
Nodule size × nodule density	42.69	<0.0001
Nodule density × scan type	20.42	<0.0001
Nodule size × scan type	10.14	<0.0001

V_m , measured nodule volume; V_{rs} , reference standard nodule volume. The mean difference between APEs = APE with filtered back projection (FBP) – APE with iterative reconstruction (IR). APE with IR was measured on images reconstructed with IR, and the APE with FBP was measured on images reconstructed with FBP.

$$APE = 100 \times |V_m - V_{rs}| / V_{rs}$$

In addition, the effect of IR was more pronounced for volume scan than helical scan ($p = 0.0005$). Significant interactions between nodule size and CT tube current and between nodule density and CT tube current were seen. They contributed significantly to the mean differences of APEs as paired variables (Figure 6a,b). The results showed that the benefit of IR was greater for the smaller ground-glass nodules scanned with

lower CT tube current. They also showed no significant effect of CT tube current on the reconstruction protocols for solid nodules.

DISCUSSION

The volumetric measurements of lung nodules have been considered increasingly important, because malignant nodules may grow asymmetrically and their growth may remain unnoticed with manual diameter measurements particularly in small lung nodules. The early lung cancer action project and national lung screening trial (NLST) were based on nodule diameter assessment. In the NLST, low-dose CT scans that revealed any non-calcified nodule measuring at least 4 mm in any diameter were classified as positive.^{20,21} However, the volume assessment and doubling time of lung cancers diagnosed in annual repeat rounds of CT screening have been also considered important and studies have been conducted based on nodule volume measurement.^{3,22} The key issues in volumetric analysis are the precision and accuracy of volumetric measurements, which depend on a number of inter-related factors. In this study, we have shown that IR significantly improved the accuracy of lung nodule volumetry compared with FBP particularly for ground-glass nodules (–630 HU). The effect of IR was more pronounced for the smaller lung nodules scanned with lower CT tube current (≤ 20 mAs), volume scan mode higher than CT tube current (≥ 30 mAs) and helical scan mode.

Many studies have revealed a number of factors affecting the accuracy of volumetric measurement, including nodule size and density, image acquisition and reconstruction parameters and measurement techniques such as algorithms for segmentation or

Table 3. Absolute percentage errors (APEs) of measured nodule volume with two image reconstruction techniques by nodule density and size

Nodule density (HU)	Nodule size (mm)	APE with IR	APE with FBP	p-value
–630	5	7.4 ± 4.1	14.9 ± 7.5	<0.0001
	8	17.2 ± 2.6	19.1 ± 4.4	0.0002
	10	8.5 ± 1.6	10.5 ± 3.9	<0.0001
	12	8.7 ± 1.9	11.8 ± 5.3	<0.0001
	Total	10.5 ± 4.8	14.1 ± 6.3	<0.0001
100	5	7.2 ± 2.1	6.7 ± 2.0	0.0596
	8	3.3 ± 1.0	2.5 ± 1.0	<0.0001
	10	4.3 ± 0.4	3.8 ± 0.4	<0.0001
	12	3.1 ± 0.3	2.7 ± 0.4	<0.0001
	Total	4.5 ± 2.0	3.9 ± 2.0	<0.0001
Total	5	7.3 ± 3.2	10.8 ± 6.8	0.0005
	8	10.3 ± 7.3	10.8 ± 8.9	0.9735
	10	6.4 ± 2.5	7.1 ± 4.3	0.3037
	12	5.9 ± 3.1	7.3 ± 5.9	0.0112
	Total	7.5 ± 4.7	9.0 ± 6.9	0.0004

FBP, filtered back projection; IR, iterative reconstruction.

Values are mean ± standard deviation of APE.

APE with IR was measured on images reconstructed with IR, and the APE with FBP was measured on images reconstructed with FBP.

Figure 3. (a) Difference of the absolute percentage error (APE) between iterative reconstruction (IR) and filtered back projection (FBP) in different nodule sizes. Columns, mean; bars, 95% confidence interval (* $p < 0.05$). (b) The effect of nodule size on the mean difference of APE (diff_APE) between IR and FBP.

software tools. There has been increasing interest in IR because it has the potential to reduce the radiation dose in CT.^{10,23,24} The noise reduction with IR probably has considerable effects on nodule segmentation and volume estimation with the expansion of semi-automated 3D tools. Among the several IR algorithms offered by different vendors, we used AIDR 3D by Toshiba Medical Systems. The AIDR 3D requires only inconsiderable additional reconstruction time by virtue of limitation of iterations only in the image space. The AIDR 3D uses a statistical noise model considering both the photon and electronic noise, to reduce the noise resulting from photon starvation in the projection data. In addition, in the image space, AIDR 3D uses a special algorithm of adaptive, weighted, anisotropic diffusion for denoising with edge preservation in order to reduce noise while maintaining edge structures and noise texture.^{23–26} Recently, several reports showed that the AIDR 3D significantly reduced image noise in coronary CT angiography and chest CT and has the potential to decrease radiation dose without compromise in image qualities.^{23,24,27,28} Previous studies^{23,24} have predicted a benefit of IR in noise and dose reduction, but this benefit is not

conferred on all volumetric measurements. In this study, we have assessed the applicability of volumetry in low-dose CT by using IR to overcome the noise from low radiation exposure and to maintain image quality. Furthermore, we evaluated the effects of nodule size, nodule density and scan type on application of IR for the accuracy of volumetric measurements.

Our statistical analysis confirmed that there were significant influences of several individual factors in volumetric measurement of pulmonary nodules on low-dose CT using IR. In fact, on the basis of F values, nodule density was the most significant individual feature, followed by CT tube current, nodule size and scan type. The most significant cross-effect was the interaction of nodule density with CT tube current. Our results support the findings of other studies predicting a benefit in noise and dose reduction with IR.^{23–27} To the best of our knowledge, this is the first detailed study conducted to evaluate the performance of volumetric measurements of lung nodules with application of IR and varying the nodule density, nodule size, CT tube current and scan type. We expect our study results will provide fundamental

Figure 4. (a) Difference of the absolute percentage error (APE) between iterative reconstruction (IR) and filtered back projection (FBP) in different nodule densities. Columns, mean; bars, 95% confidence interval (* $p < 0.05$). (b) The effect of nodule density on the mean difference of APE (diff_APE) between IR and FBP.

Table 4. Absolute percentage errors (APEs) of measured nodule volume with two image reconstruction techniques by nodule density and CT tube current

Nodule density (HU)	CT tube current (mAs)	APE with IR	APE with FBP	<i>p</i> -value
−630	10	11.8 ± 5.9	21.3 ± 6.1	<0.0001
	20	10.1 ± 5.3	13.2 ± 4.5	<0.0001
	30	10.8 ± 3.9	11.6 ± 3.9	0.0233
	50	9.3 ± 3.4	10.2 ± 3.9	0.0116
	Total	10.5 ± 4.8	14.1 ± 6.3	<0.0001
100	10	4.3 ± 1.9	3.8 ± 2.2	0.0002
	20	4.1 ± 1.6	3.6 ± 2.0	0.0005
	30	5.1 ± 2.6	4.4 ± 2.2	<0.0001
	50	4.4 ± 1.9	3.9 ± 1.6	<0.0001
	Total	4.5 ± 2.0	3.9 ± 2.0	<0.0001
Total	10	8.1 ± 5.7	12.6 ± 9.9	<0.0001
	20	7.1 ± 4.9	8.4 ± 5.9	0.0034
	30	7.9 ± 4.4	8.0 ± 4.8	0.4835
	50	6.9 ± 3.6	7.1 ± 4.3	0.6872
	Total	7.5 ± 4.7	9.0 ± 6.9	0.0004

FBP, filtered back projection; IR, iterative reconstruction.

Values are mean ± standard deviation of APE.

APE with IR was measured on images reconstructed with IR, and the APE with FBP was measured on images reconstructed with FBP.

information for clinical application and research regarding lung nodule volumetry in low-dose CT.

Nodule density strongly affected the accuracy of volumetry as shown in previous studies.^{15,16,29,30} Despite the clinical importance of radiologic attenuation, only a small number of studies have reported volumetric measurement results on ground-glass nodules, possibly owing to the lack of dedicated software that can accurately segment lesions with low contrast and uneven boundaries. Ko et al¹⁶ showed that absolute error values were higher for ground-glass nodules than for solid nodules. Volumetry of

ground-glass nodules is difficult because the attenuation difference between these nodules and normal lung parenchyma is small,²⁹ and they usually have less distinct boundaries with the surrounding lung parenchyma than solid nodules.³⁰ In our study, overall volume measurement of solid nodules generally resulted in more accurate volume estimates than for ground-glass nodules. We have also shown that IR contributed to the improvement of accuracy, with a significantly lower APE of 10.5 ± 4.8% than that of 14.1 ± 6.3% for FBP in ground-glass nodules ($p < 0.0001$). However, our results show that the benefit of IR was not consistent across all nodule densities. For ground-

Figure 5. (a) Difference of the absolute percentage error (APE) between iterative reconstruction (IR) and filtered back projection (FBP) in different CT tube currents. Columns, mean; bars, 95% confidence interval (* $p < 0.05$). (b) The effect of CT tube current on the mean difference of APE (diff_APE) between IR and FBP.

Figure 6. (a) The effect of interactions between nodule size and CT tube current and (b) nodule density and CT tube current on the mean difference of the absolute percentage error (diff_APE) between iterative reconstruction and filtered back projection. Error bars, 95% confidence interval.

glass nodules of -630 HU, IR has clear benefit, whereas for solid nodules of $+100$ HU, it does not. To the best of our knowledge, no reports have been published on the dependence of volumetry on lesion density with IR for lung nodules. Because ground-glass opacities are shown in lower contrast and IR increases low-contrast detectability in a low-dose protocol, the benefit of IR in detection is more pronounced for ground-glass than solid nodules. Higuchi et al³¹ reported that small ground-glass nodules could not be visualized because they were obscured because of high noise with low-dose CT with FBP. By contrast, the detectability of ground-glass nodules tended to be slightly improved with IR because of noise reduction effects and artefact prevention. Moreover, IR makes it possible to maintain accurate density measurements of regions of interest even at low effective milliamp per second (mAs). While more work is needed to assess volumetric error as a function of nodule density, we consider that the effect of IR, which increases low-contrast detectability, can render the margins of ground-glass nodules more distinctly for more accurate automatic segmentation. Recently,

Willeminck et al¹⁷ reported no clinically relevant differences between lung nodule volumes that were measured at reduced tube voltage and current for both FBP and IR in the case of solid nodules. Our results suggest that the volumetry of solid nodules tends to be slightly more accurate with FBP, but not to a clinically relevant extent. We assume that solid nodules have high contrast, and that their automatic segmentation is less influenced by lower dose and noise.

With regard to CT tube current, several studies have examined the effect of radiation dose on volumetric measurement error. While the bias error was significantly smaller for standard-dose than that for low-dose scans in one study,¹⁶ others showed no significant effect of radiation dose on volumetric error.¹⁸ However, the effect of radiation dose on volumetric measurement in relation to nodule density and image reconstruction technique has not been investigated. For ground-glass nodules, the APE was increased as CT tube current decreased, which was $21.3 \pm 6.1\%$ with FBP at 10 mAs. Additionally, the effect of IR was more pronounced for

the lower dose. Our results showed an advantage for IR at 10 and 20 mAs, which resulted in significantly lower bias than FBP. The APE for ground-glass nodules even at 10 mAs with IR remained at $11.8 \pm 5.9\%$. In other words, IR makes it possible to reduce CT tube current settings without significantly reducing the accuracy of volumetric assessment.

Nodule size is also an important factor in volumetric measurement because smaller nodules have a larger proportion of surface voxels that are affected by the partial volume effect.¹¹ An increase of nodule volume estimation error with decreasing nodule size was shown in two studies.^{12,32} Our study showed that the APE of the 5-mm solid nodule was larger than that of the nodules ≥ 8 mm. For ground-glass nodules, the highest error was shown in 8-mm nodules, possibly owing to unstable segmentation of the attached vessels. For most of the ground-glass nodules in this study, segmentation led to underestimated volumes. However, the irregular performance of the segmentation software further led to vessel-induced overestimation in small ground-glass nodules, which compensated for their volume underestimation, and decreased the error. Nonetheless, this may not change the result of the significant effect of nodule size on application of IR; rather, we feel that the effect of IR in decreasing volumetric error in small ground-glass nodules is greater than that of inaccurate segmentation of the attached vessels.

There were several limitations in this study. First, lung nodule volume measurement was performed without manual adjustment. This allows unstable automatic segmentation of attached vessels in the smallest ground-glass nodules. Vessel attachments were found to greatly impact volume quantification in previous studies, leading to segmentation failures, particularly for small nodules.¹⁵ However, we performed this method to minimize the influence of observers and this eliminated predictable variations

caused by observer's manual segmentation. Second, all simulated lung nodules were spherical in shape, with sharp margins, and within a chest phantom, which eliminates complicating factors in the real clinical field such as different lung nodule morphology, motions of breathing and cardiac beats, different body sizes and different locations within the thorax. Among various affecting factors regarding lung nodules, we only selected and focused on nodule size and density as affecting factors in this phantom study. Therefore, the accuracy of lung nodule volumetry in this phantom study is better than that in an *in vivo* study. Further study will be needed for nodule morphology and real lung nodules *in vivo*. Third, although lung nodule volumetry is affected by many CT parameters, this study analysed effects of low CT tube current as a factor of CT parameters in addition to nodule size and density.

In conclusion, lung nodule volumetry using low-dose CT is accurate, and remained reliable even for small ground-glass nodules at lower CT tube current by application of IR in this phantom study. The effect of IR was more pronounced for smaller nodules. IR improves the accuracy of nodule volumetry in ground-glass nodules with lower CT tube current than FBP. The lung nodule volumetry in low-dose CT is more accurate with a reasonable error range with application of IR, and application of IR is more helpful even in smaller nodules, ground-glass nodules and lower CT tube current.

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