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Abstract. Task-based assessment of computed tomography (CT) image quality requires a large number of cases with ground truth. Prospective case acquisition can be time-consuming. Inserting lesions into existing cases to simulate positive cases is a promising alternative. The aim was to evaluate a recently developed projection-based lesion insertion technique in thoracic CT. In total, 32 lung nodules of various attenuations were segmented from 21 patient cases, forward projected, inserted into projections, and reconstructed. Two experienced radiologists and two residents independently evaluated these nodules in two substudies. First, the 32 inserted and the 32 original nodules were presented in a randomized order and each received a score from 1 to 10 (1 = absolutely artificial to 10 = absolutely realistic). Second, the inserted and the corresponding original lesions were presented side-by-side to each reader. For the randomized evaluation, discrimination of real versus inserted nodules was poor with areas under the receiver operative characteristic curves being 0.57 [95% confidence interval (CI): 0.46 to 0.68], 0.69 (95% CI: 0.58 to 0.78), and 0.62 (95% CI: 0.54 to 0.69) for the two residents, two radiologists, and all four readers, respectively. Our projection-based lung nodule insertion technique provides a robust method to artificially generate positive cases that prove to be difficult to differentiate from real cases. © 2017 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: [10.1117/1.JMI.4.1.013510](https://doi.org/10.1117/1.JMI.4.1.013510)]

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1 Introduction

A large number of cases with positive findings are typically needed to perform task-based assessment of image quality and radiation dose optimization in computed tomography (CT).¹ These cases can be collected prospectively through carefully designed clinical trials or retrospectively by querying a large number of archived clinical exams. For example, in a recent multicenter study to evaluate the dose reduction potential of an iterative reconstruction (IR) in a lung nodule detection task, over 100 patients with known or suspected lung tumors were prospectively collected, yielding 221 nodules for the study.² However, this case collection process can be very time and resource intensive, and it can be challenging to establish the diagnostic truth. As an alternative approach, one can artificially generate a large number of patient cases with positive findings by inserting lesions into existing normal patient cases. Although it can be difficult to assume normality with 100% certainty with clinical cases, this approach is efficient and the truth of lesion characteristics [e.g., size, shape, attenuation (CT number)] can be readily established.

Most of the existing lesion insertion techniques were performed in image domain after image reconstruction.^{3–7} As these methods directly insert lesions on reconstructed images, it is very challenging to render the appearances of lesions in relation to neighboring structures to accurately reflect the impact of CT acquisition and reconstruction process, rendering the assessment results of clinical CT image quality questionable. We recently developed a raw-data-based lesion insertion

technique⁸ that allows segmented lesions from patients to be reinserted back into the same patient projection data prior to image reconstruction. Since the lesion is added in the projection data, the impact of image reconstruction on the lesion appearance and noise texture is inherently incorporated after reconstruction, which is a critical step to mimicking the realistic appearance of the lesion. In addition, one can specify the lesion characteristics (location, size, shape, attenuation, and nodule type) so that the diagnostic task can be well controlled, providing an efficient way to create a large number of cases for evaluating a specific task. This technique can be used on any state-of-the-art commercial CT scanners in both axial and helical modes given that the CT projection data are available and can be interpreted by users. The technique has been validated in a phantom study for CT number accuracy and high contrast spatial resolution.⁸

In a clinical observer study, the insertion technique was validated for liver lesions in abdominal CT.⁹ In that study, radiologists evaluated the inserted liver lesions and the real ones both in a randomized scoring study and a side-by-side comparison study. The results demonstrated that they could not distinguish between inserted and real liver lesions in both observer studies. However, unlike lesion insertion in abdominal organ, such as liver, where there is low contrast between the solid liver and the solid lesion, lung nodule insertion is highly challenging due to marked inherent contrast between solid and part solid nodules and the air-filled lung parenchyma. In addition, the inherent variations in nodule densities (solid, groundglass, and part solid nodules) further add to the difficulty. Therefore,

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Fig. 1 Projection-domain lesion insertion process.

whether the lesion insertion technique is still valid for lung nodule insertion in thoracic CT remains to be investigated, especially considering that there has been growing interest in quantitative evaluation of lung nodule characteristics¹⁰ and optimizing radiation dose in lung cancer screening CT using various reconstruction and data acquisition techniques. Our nodule insertion technique in projection data domain may provide a powerful tool for designing efficient observer studies for these purposes.

Before the projection-based lesion insertion technique can be used for this purpose, the validity of lung nodule insertion needs to be evaluated by radiologists. As such, the aim of the current study was to validate this pulmonary nodule insertion technique by evaluating how realistic the inserted nodules in existing CT exams appear to radiologists in an observer study.

2 Methods

2.1 Projection Domain Lesion Insertion Technique

The projection-domain lesion insertion technique was described in detail in Ref. 8. A brief overview is provided below.

First, the raw data acquired from patient exams on a clinical CT scanner were decoded with software provided by the vendor under a research agreement (Siemens Healthcare). Two types of information were obtained: (1) CT acquisition parameters, including tube potential, tube current, projection angle, CT gantry geometry, and table position. Detailed information in regard to the flying focal spot was also acquired, which is necessary to determine the exact geometry of the data acquisition that is needed in the forward projection. (2) Projection data at each

projection view, which were in the form of line integral of linear attenuation coefficient along each x-ray path. The data were already processed by the scanner to correct for dark field, gain, and beam hardening.

Second, for a given lesion that was either a real one directly segmented from patients or an inserted one after digital processing, a forward projection program was used to generate the projection data based on the geometry of the CT scanner and the scanning parameters (detector configuration, helical pitch, kV, etc.) for that specific exam. The forward projection assumed a point source and point detector geometry. A monochromatic x-ray beam at 70 keV was used, which was the energy for beam-hardening correction. Since the forward projection program mathematically simulated the CT acquisition process, the lesion projection data were similar to what would be acquired by physically scanning the lesion. In addition, the lesion is small compared to the patient body size, so it was assumed that the impact of lesion presence on overall noise of the image is negligible and there was no noise added during the forward projection of the lesion. The lesion projection data were subsequently added into the original patient projection data for each corresponding projection view. The modified projection data were then written back in the original data format and loaded onto the scanner for image reconstruction. A flowchart of the lesion insertion process is shown in Fig. 1.

2.2 Lung-Nodule Insertion in Patient Cases

The patient cases used in this study were collected under the institutional review board (IRB) approval at Mayo Clinic in Rochester, Minnesota (IRB #11-000248) and was compliant

Table 1 List of nodule size (diameter), attenuation (CT number), and nodule type of the 32 nodules used in this study.

Patient number	Nodule number	Diameter (mm)	CT # (HU)	Nodule type
1	1	5.1	−275	Solid
	2	6.7	−216	Solid
2	3	3.9	−301	Solid
3	4	5.3	−46	Solid
4	5	6	−580	Part-solid
5	6	6.4	−76	Solid
6	7	6.9	−1	Solid
7	8	6	19	Calcified granuloma
8	9	10.9	−34	Solid
	10	7.1	−16	Solid
9	11	12.3	−13	Solid
10	12	8.2	−339	Part-solid
11	13	7.6	1095	Calcified granuloma
	14	6.9	−2	Solid
12	15	6.6	−63	Solid
13	16	3.4	−199	Solid
	17	3.5	676	Calcified granuloma
	18	3.4	−442	Part-solid
	19	2.4	−223	Solid
14	20	10.9	7	Solid
15	21	6.8	−361	Solid
	22	7.3	−191	Solid
	23	4.5	−138	Solid
	24	7.5	−450	Part-solid
17	25	10.2	−8	Solid
18	26	4.7	−97	Solid
	27	9.3	−18	Solid
19	28	5.4	−660	Pure ground glass
	29	6.7	−60	Solid
20	30	4.2	−72	Solid
21	31	4	−277	Solid
	32	6.9	4	Solid

with HIPAA guidelines. The requirement for informed consent was waived for this retrospective study. Twenty-one thoracic CT exams were retrospectively selected by an experienced thoracic radiologist (C.W.K.) with 11 years of experience from a patient raw-data library consisting of 44 thoracic CT exams. The rest of the cases were excluded because the nodules were localized in locations that are difficult to segment. These exams were performed on a 128-slice CT scanner (Somatom Definition Flash, Siemens Healthcare) using a routine chest protocol (128×0.6 mm, 120 kV, 0.28 s rotation time, a quality reference mAs of 140, and nominal CTDIvol 9.4 mGy). Images were reconstructed with 1.5 mm image slice thickness and 1 mm increment using a medium-sharp kernel (B46f). In total, 32 nodules were identified and segmented from these 21 cases. The nodule size, attenuation (in terms of CT number), and nodule type are listed in Table 1.

Nodule boundaries were manually drawn slice-by-slice using an open-source software (Seg3D, University of Utah, Salt Lake City, Utah), under the guidance of an experienced thoracic radiologist (C.W.K.). The nodule boundaries were slightly larger than the edge of the lesions to ensure that all the visible parts of lesions were included. The same radiologist also specified a new location for the nodule to be reinserted. The nodule was inserted into the same patient data using the following rules: (1) at a different anatomical location and a different slice, (2) have the nodule abut a small blood vessel (solid, but fainter, white lines), (3) do not cross an airway or fissure, (4) if possible, orient oval nodules so the long axis is oriented radially from the center of the chest. The radiologist who segmented the nodule and determined the locations for nodule insertion did not participate in the observer study.

The final database yielded 64 nodules from 21 patient cases, including 32 original nodules and 32 inserted nodules. Figure 2 shows examples of inserted lung nodules of different sizes, attenuation, and shapes.

2.3 Observer Study

Two experienced radiologists, one with 20 years and the other 27 years of experience in thoracic radiology, and two radiology residents with 2 and 4 years of experience, respectively, participated in an observer study to evaluate how well they could differentiate between real and inserted nodules. The observer study was divided into two substudies: a randomized scoring study and a two-alternative-forced-choice (2AFC) study. For both studies, the readers were informed of the lesion location.

2.3.1 Randomized scoring study

In this substudy, each of the 32 inserted and 32 real nodules were presented to the four readers independently in a randomized order. The authenticity of the nodules was blinded to the readers. For each nodule, the readers were allowed to navigate back and forth multiple slices surrounding the nodule similar to a realistic clinical setting. They were also allowed to change display window settings, e.g., from the default lung window setting (window level = −600 HU and window width = 1500 HU) to soft tissue window setting (window level = 40 HU and window width = 400 HU). Each reader reviewed the nodules independently and provided a rating score from 1 to 10 (1 = absolutely artificial to 10 = absolutely realistic, each score point in between representing a different confidence level, Table 2) for the realism of each lesion. The study was conducted

Fig. 2 Examples of inserted lung nodules with different sizes, attenuation, and shapes: (a) solid, (b) part-solid, and (c) ground glass nodules. The display window width is 1500 HU and the window level is -600 HU.

on a dual-monitor workstation (Advantage Workstation, GE Healthcare, Waukesha, Wisconsin) with one monitor activated for the randomized scoring study and both monitors used for the 2AFC study below. The monitors were calibrated according to the American College of Radiology standards.¹¹ The ambient lighting was kept constant to a comfortable level to the readers. The readers were advised to take breaks when needed to avoid fatigue, and no time constraint was set for the readers.

2.3.2 Two-alternative-forced-choice study

In addition to the randomized scoring study, a 2AFC study was also performed as a supplemental test to explore the limit of the lesion insertion algorithm. The 2AFC test is frequently used as an established controlled measure of observers' abilities to distinguish between two classes,¹² which represents a more challenging test than the randomized scoring test. For the current evaluation, the inserted and the corresponding real nodules were presented side-by-side on the dual-monitor workstation with both monitors active. The readers were allowed to scroll back and forth multiple slices surrounding each nodule and to change display window settings. The readers identified which monitor contained the inserted nodule and provided a confidence score (1 = no confidence at all to 5 = completely certain,

Table 2 Rating scale for nodule assessment in the randomized scoring study.

Score	Definition
1	100% confidence that the lesion is not real
2	Very doubtful that the lesion is real
3	
4	Unlikely that the lesion is real
5	
6	Very unsure whether the lesion is real or not
7	
8	Likely that the lesion is real
9	Very likely that the lesion is real
10	100% confidence that the lesion is real

Table 3 Rating scale for nodule assessment in the 2AFC study.

Confidence level	Definition
1	No confidence in determination
2	Possibly correct
3	Probably correct
4	Likely correct
5	100% confidence in determination

Table 3). For each reader, the 2AFC study was conducted after the randomized scoring study.

2.4 Statistical Analysis

For the randomized scoring study, we calculated the mean and standard deviation of the confidence scores for both real and inserted nodules for the two radiology residents, two radiologists, and all four readers. The receiver operative characteristic (ROC) analysis was performed using an ROC calculator¹³ that was adopted from the ROCFIT program by Metz.¹⁴ The ROC curves were fitted by using a binomial model. The 95% confidence interval (CI) of the ROC curve and the area under

Table 4 Mean and standard deviation of the confidence score for both real and inserted nodules, the AUC and its corresponding 95% CI values, for the two residents, two radiologists, and all readers.

	Scores for real nodules (mean $\pm$ stdev)	Scores for inserted nodules (mean $\pm$ stdev)	AUC	95% CI
Resident 1	5.6 $\pm$ 3.2	6.1 $\pm$ 3.4	0.45	0.29 to 0.62
Resident 2	7.4 $\pm$ 2.6	5.0 $\pm$ 2.9	0.73	0.57 to 0.86
Radiologist 1	6.7 $\pm$ 2.3	4.3 $\pm$ 2.0	0.78	0.62 to 0.88
Radiologist 2	6.1 $\pm$ 2.8	4.9 $\pm$ 2.4	0.62	0.45 to 0.77
Two residents	6.5 $\pm$ 3.0	6.3 $\pm$ 3.2	0.57	0.46 to 0.68
Two radiologists	6.4 $\pm$ 2.5	4.6 $\pm$ 2.6	0.69	0.58 to 0.78
All four readers	6.4 $\pm$ 2.8	5.1 $\pm$ 2.8	0.62	0.54 to 0.69

the ROC curve (AUC) were calculated, which were used as the metric to evaluate how well the observers can differentiate between real and inserted nodules. A value of AUC close to 0.5 indicates that it is challenging for observers to differentiate. For the 2AFC study, the percent of correctly identified nodule pairs was calculated. The distributions of the confidence score for correctly and incorrectly identified nodules pairs were determined.

3 Results

3.1 Randomized Scoring Study

The mean and standard deviation of the confidence score for both real and inserted nodules, the AUC and its corresponding

95% CI values, individually for the four readers, pooled for the two residents and two radiologists, and all readers are summarized in Table 4. Differentiation of real versus inserted nodules was poor with AUC being 0.57 (95% CI: 0.46 to 0.68), 0.69 (95% CI: 0.58 to 0.78), and 0.62 (95% CI: 0.54 to 0.69) for the two residents, two radiologists, and all four readers grouped together, respectively (Fig. 3). Figure 4 shows sample cases with real and inserted lesions receiving similar scores, which demonstrated that readers were not able to differentiate between the real and inserted lesions.

In the 2AFC study, the two radiologists correctly identified inserted lesions in 55/64 pairs, the confidence score was moderate (2.4 out of 5). Among those correctly identified nodules (55), only 16 of them had a confidence score greater

Fig. 3 Fitted ROC curves (blue) and 95% CIs for (a) radiology resident 1, (b) radiology resident 2, (c) radiologist 3, (d) radiologist 4, (e) two radiology residents, (f) two radiologists, and (g) all four readers, representing how well the readers can differentiate inserted lesions from the real ones.

Fig. 4 Exemplary cases where radiologists were unable to differentiate real from inserted nodules in the randomized scoring study. The scores listed under each image were from: resident 1, resident 2, radiologist 1, and radiologist 2.

than 3. Similarly, the two residents were correct in 48/64 pairs with a confidence score of 2.7 out of 5. Among those correctly identified nodules (48), only 17 of them had a confidence score greater than 3. Figure 5(a) shows the distribution of confidence score for correctly identified nodules for residents, radiologists, and all readers combined, Fig. 5(b) shows the distribution of confidence score for incorrectly identified nodules for residents, radiologists, and all readers combined. Among those incorrectly identified nodules (25), only 1 of them had a confidence score greater than 3. Figure 6 shows image examples of real and inserted lesion pairs that received low confidence scores (confidence score ≤ 2) and at least one reader incorrectly classified the lesion pair.

Figure 7 demonstrates image examples of real and inserted nodule pairs that all readers correctly classified and received high confidence scores (≥ 3). In the first example, the original real lesion on the left is connected to the pleura because of pleural reaction resulting in changes of the associated pleural contour (pleura tag); while the inserted lesion does not have a convincing relationship with the pleura, in addition to the

unrealistic relationship with surrounding small vessels (better visualized when scrolling multiple slices). In the second example, the readers thought that the location of the inserted lesion and the relationship with the vessels seem artificial when compared with the real lesion; however, when viewed individually in the random score test, they cannot be effectively differentiated (mean score difference is ± 1.8).

4 Discussions

We have validated a projection-based lesion insertion technique recently developed in our group for lung nodule insertion in thoracic CT. To the best of our knowledge, the evaluated lesion insertion tool was the first to insert segmented patient lesions into real patient raw data to simulate positive cases. The validation of inserted lung nodules performed in this study may facilitate efficient and quantitative virtual clinical trials to optimize image quality and radiation dose in thoracic CT and lung-cancer screening CT.

The observer study demonstrated that it is difficult for thoracic radiologists to differentiate between inserted and real nodules, especially when the nodules are displayed randomly to the radiologists. The ROC analysis for the randomized scoring study showed that the AUC for all four readers together was 0.62 (95% CI: [0.54, 0.69]), which was close to random guess and is commonly considered as “bad classification.”¹⁵ The confidence scores for inserted and real nodules were 5.1 ± 2.8 and 6.4 ± 2.8 , respectively, both within the range of the ranking scale: “Very unsure whether the lesion is real or not” (Table 2).

In the 2AFC study, where the real nodule in its original location and the inserted nodule were displayed side-by-side, we observe that radiologists were able to identify correctly the inserted nodule for majority of the cases, although the confidence level was not high. These results were drastically different from those obtained in the 2AFC study of liver lesion insertion in abdominal CT, which was performed by our group in a similar study design.⁹ In the previous liver lesion insertion study, the abdominal radiologists were unable to correctly distinguish the inserted from the real lesions in 25 of 51 (49%) pairs. The reason why radiologists were able to better differentiate between inserted and real nodules in the 2AFC study in the lung was because the radiologists can directly compare side-by-side how the two nodules relate to the surrounding pulmonary structures. When a nodule is inserted, its connection with the surrounding vasculatures is difficult to control and thus the realistic appearance may be degraded slightly, especially when the original nodule is available as the reference. In addition, the contrast of the nodule relative to the lung background is high, which makes any inappropriate connection with the surrounding structures more obvious when the original nodule is available for comparison. For liver lesion insertion, however, the contrast level of the lesion relative to the background is much lower (between -132 and 130 HU) and the liver background is relatively more uniform than the lung background, which makes the blending of the liver lesion into the background easier than the lung nodules. This effect shows that the nodule insertion in thoracic CT is more challenging than liver lesion insertion in abdominal CT. However, the 2AFC study, being a strict test, is not likely to be used as a format in an application of nodule insertion. Most likely, the patient cases with inserted nodules are presented to radiologists for evaluating diagnostic performance without the need of showing the original nodules. In that

Fig. 5 Distribution of confidence scores for (A) correctly and (B) incorrectly identified nodules for (a) residents, (b) radiologists, and (c) all readers combined in the 2AFC study.

Fig. 6 Examples of real and inserted lesions with confidence score ≤ 2 and at least one reader incorrectly classified the lesion pair in the 2AFC study.

situation, as demonstrated in the randomized scoring study, radiologists cannot differentiate between inserted and real nodules.

Several image-domain nodule insertion techniques were developed and validated in previous studies.³⁻⁷ Pezeshk et al.⁷ developed an image-domain nodule insertion tool based on a Poisson editing approach. To accommodate the noise difference between inserted nodule and surrounding background structure, they also introduced an image-based noise transfer scheme in their technique. The uniqueness of our projection-domain nodule insertion technique is that the impact of image reconstruction on nodule characteristics and noise can be readily incorporated.

Fig. 7 Examples of real and inserted lesion pairs that all readers correctly classified and received high confidence scores (≥ 3).

With the wide use of various nonlinear IR and noise reduction techniques on clinical CT scanners,^{16,17} it is important to evaluate the image quality and dose reduction potential of those techniques.^{18,19} Image domain nodule insertion added nodules onto the images after image reconstruction and noise reduction, which cannot readily incorporate the change of noise and spatial resolution introduced by the reconstruction process. Another benefit of projection-domain nodule insertion is that it can work well together with projection-domain noise insertion techniques to simulate multiple dose levels. By inserting the lesion in projection domain, the noise insertion can easily generate appropriate noise level and texture on the lesion corresponding to the desired dose level to be simulated. In comparison, when the lesion is inserted in image domain, there is a need to estimate the noise level and texture on the lesion itself before it can be inserted, and this estimate may be very challenging especially when nonlinear IR algorithms are used.

There are many potential applications of the nodule insertion techniques validated in this study. One can insert nodules to a large number of negative cases to create various case libraries, which can be used for various applications related to task-based performance evaluation. For example, radiologists can evaluate the nodule detectability with different reconstruction and noise reduction algorithms; together with noise insertion and low-dose simulation,^{20,21} the dose reduction potential can be quantitatively evaluated for the task of nodule detection. One can also evaluate the quantitative accuracy of volume and size measurement of nodules at different reconstruction and radiation dose configurations.^{10,22,23} With known truth of nodule size and volume, the task becomes much easier than using real patient cases. In this type of applications, one could digitally create nodules with size and volume exactly known, instead of using nodules segmented from patient images, where the truth of nodule size and volume remains uncertain. Another important benefit of nodule insertion technique in the aforementioned applications is that, based on nodules segmented from real patient cases, one can readily change the nodule shape, size, and attenuation digitally, which provides great flexibility of controlling the distribution of nodule characteristics in the case library that is difficult to achieve in real patient case collection.

This study has limitations. First, we have not evaluated the performance at the low dose level in lung cancer screening CT. The current evaluation was performed using thoracic CT cases acquired at routine dose level, which is much higher than that in lung cancer screening CT.²⁴ The evaluation at higher dose level in the current study actually presented more challenges. At the routine dose level, the noise is lower and many subtle structures in lung are more visible than at the screening dose level. Therefore, it is expected that the inserted and real nodules would become more indistinguishable at the screening dose level. Second, the number of nodules evaluated was relatively small, which was limited by the positive cases available to us. Finally, the accuracy of lesion insertion cannot be claimed with absolute certainty due to the complexity of image formation process in CT (e.g., beam hardening, scattering, and nonlinear partial volume). Unless we know the absolute truth of the original subject and the nodule and can simulate accurately from the very early stage of the image formation process, one can only expect to achieve relatively accurate simulation. Lesion insertion in projection domain evaluated in this study can achieve such relative accuracy by at least incorporating the image reconstruction into the process, which is critically important since that will

mimic the realistic appearance of the noise texture in the nodule along with surrounding tissues.

5 Conclusions

We performed an observer study to assess the realism of lung nodules simulated using a newly developed projection-domain lesion insertion technique. Our results showed that the artificially generated lung nodules were difficult to be differentiated from real nodules by even highly experienced radiologists, indicating that the projection-domain lesion insertion technique can be used to create patient cases with realistic-appearing nodules.

Disclosures

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References

1. J. G. Fletcher et al., "Observer performance in the detection and classification of malignant hepatic nodules and masses with CT image-space denoising and iterative reconstruction," *Radiology* **276**, 465–478 (2015).
2. Y. Nagatani et al., "Lung nodule detection performance in five observers on computed tomography (CT) with adaptive iterative dose reduction using three-dimensional processing (AIDR 3D) in a Japanese multicenter study: comparison between ultra-low-dose CT and low-dose CT by receiver-operating characteristic analysis," *Eur. J. Radiol.* **84**, 1401–1412 (2015).
3. M. T. Madsen et al., "A new software tool for removing, storing, and adding abnormalities to medical images for perception research studies," *Acad. Radiol.* **13**, 305–312 (2006).
4. X. Li et al., "Three-dimensional simulation of lung nodules for paediatric multidetector array CT," *Br. J. Radiol.* **82**, 401–411 (2009).
5. C. L. Hoe et al., "Simulation of liver lesions for pediatric CT," *Radiology* **238**, 699–705 (2006).
6. J. Solomon and E. Samei, "A generic framework to simulate realistic lung, liver and renal pathologies in CT imaging," *Phys. Med. Biol.* **59**, 6637–6657 (2014).
7. A. Pezeshk et al., "Seamless insertion of pulmonary nodules in chest CT Images," *IEEE Trans. Biomed. Eng.* **62**, 2812–2827 (2015).
8. B. Chen et al., "Lesion insertion in the projection domain: methods and initial results," *Med. Phys.* **42**, 7034–7042 (2015).
9. B. Chen et al., "Validation of a projection-domain insertion of liver lesions into CT Images," *Acad. Radiol.* **23**, 1221–1229 (2016).
10. "Quantitative Imaging Biomarkers Alliance (QIBA)," 2017, <http://www.rsna.org/QIBA/> (21 March 2017).
11. ACR Electronic Practice Guideline, "ACR technical standard for electronic practice of medical imaging," 2007, <https://www.acr.org/-/media/AF1480B0F95842E7B163F09FICE00977.pdf> (21 March 2017).
12. E. Lapid, R. Ulrich, and T. Rammsayer, "On estimating the difference limen in duration discrimination tasks: a comparison of the 2AFC and the reminder task," *Percept. Psychophys.* **70**, 291–305 (2008).
13. C. Kremser et al., "Assessing tumor perfusion and treatment response in rectal cancer," *Radiology* **238**, 756–757 (2006).
14. C. E. Metz, "ROC methodology in radiologic imaging," *Invest. Radiol.* **21**, 720–733 (1986).
15. W. Zhu, N. Zeng, and N. Wang, "Sensitivity, specificity, accuracy, associated confidence interval and ROC analysis with practical SAS[®] implementations," in *NESUG Proc.: Health Care and Life Sciences*, Baltimore, Maryland (2010).

16. A. K. Hara et al., "Iterative reconstruction technique for reducing body radiation dose at CT: feasibility study," *Am. J. Roentgenol.* **193**, 764–771 (2009).
17. E. C. Ehman et al., "Noise reduction to decrease radiation dose and improve conspicuity of hepatic lesions at contrast-enhanced 80-kV hepatic CT using projection space denoising," *Am. J. Roentgenol.* **198**, 405–411 (2012).
18. C. H. McCollough et al., "Degradation of CT low-contrast spatial resolution due to the use of iterative reconstruction and reduced dose levels," *Radiology* **276**, 499–506 (2015).
19. K. Li et al., "Statistical model based iterative reconstruction in clinical CT systems. Part III. Task-based kV/mAs optimization for radiation dose reduction," *Med. Phys.* **42**, 5209–5221 (2015).
20. L. Yu et al., "Development and validation of a practical lower-dose-simulation tool for optimizing computed tomography scan protocols," *J. Comput. Assisted Tomogr.* **36**, 477–487 (2012).
21. P. Massoumzadeh et al., "Validation of CT dose-reduction simulation," *Med. Phys.* **36**, 174–189 (2009).
22. B. Chen et al., "Quantitative CT: technique dependence of volume estimation on pulmonary nodules," *Phys. Med. Biol.* **57**, 1335–1348 (2012).
23. B. Chen et al., "Volumetric quantification of lung nodules in CT with iterative reconstruction (ASiR and MBIR)," *Med. Phys.* **40**, 111902 (2013).
24. D. R. Aberle et al., "The national lung screening trial: overview and study design," *Radiology* **258**, 243–253 (2011).

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