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ORIGINAL ARTICLE

Prospective Study

Ultra-low-dose chest computed tomography with model-based iterative reconstruction in the analysis of solid pulmonary nodules: A prospective study

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Abstract

BACKGROUND

Incidental pulmonary nodules are an increasingly common finding on computed tomography (CT) scans of the thorax due to the exponential rise in CT examinations in everyday practice. The majority of incidental pulmonary nodules are benign and correctly identifying the small number of malignant nodules is challenging. Ultra-low-dose CT (ULDCT) has been shown to be effective in diagnosis of respiratory pathology in comparison with traditional standard dose techniques. Our hypothesis was that ULDCT chest combined with model-based iterative reconstruction (MBIR) is comparable to standard dose CT (SDCT) chest in the analysis of pulmonary nodules with significant reduction in radiation dose.

AIM

To prospectively compare ULDCT chest combined with MBIR with SDCT chest in the analysis of solid pulmonary nodules.

METHODS

A prospective cohort study was conducted on adult patients (n = 30) attending a respiratory medicine outpatient clinic in a tertiary referral university hospital for surveillance of previously detected indeterminate pulmonary nodules on SDCT

chest. This study involved the acquisition of a reference SDCT chest followed immediately by an ULDCT chest. Nodule identification, nodule characterisation, nodule measurement, objective and subjective image quality and radiation dose were compared between ULDCT with MBIR and SDCT chest.

RESULTS

One hundred solid nodules were detected on ULDCT chest and 98 on SDCT chest. There was no significant difference in the characteristics of correctly identified nodules when comparing SDCT chest to ULDCT chest protocols. Signal-to-noise ratio was significantly increased in the ULDCT chest in all areas except in the paraspinal muscle at the maximum cardiac diameter level ($P < 0.001$). The mean subjective image quality score for overall diagnostic acceptability was 8.9/10. The mean dose length product, computed tomography volume dose index and effective dose for the ULDCT chest protocol were 5.592 mGy.cm, 0.16 mGy and 0.08 mSv respectively. These were significantly less than the SDCT chest protocol ($P < 0.001$) and represent a radiation dose reduction of 97.6%.

CONCLUSION

ULDCT chest combined with MBIR is non-inferior to SDCT chest in the analysis of previously identified solid pulmonary nodules and facilitates a large reduction in radiation dose.

Key Words: Ultra-low dose computed tomography; Solid pulmonary nodules; Computed tomography methods; Radiation dosage; Adult human

Core Tip: Recent advancements in computed tomography (CT) hardware and software have facilitated the development of ultra-low-dose imaging protocols that have the potential to significantly reduce radiation dose while, crucially, maintaining image quality and diagnostic integrity. Previously identified indeterminate solid pulmonary nodules may be effectively monitored with ultra-low-dose CT chest with the added benefit of a large reduction in radiation dose.

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INTRODUCTION

Incidental pulmonary nodules are an increasingly common finding in routine patient care secondary to the exponential rise in utilisation of chest computed tomography (CT)[1,2]. The majority of incidental pulmonary nodules are benign and correctly identifying malignant nodules poses a diagnostic challenge[3]. Based on various morphological nodule metrics, indeterminate solid pulmonary nodules are frequently followed with serial chest CT to monitor for changes that may represent malignancy. Typical solid pulmonary nodule features that correlate with likelihood of malignancy include size, internal features (*e.g.* cavitation), border characteristics (*e.g.* smooth, spiculated) and perinodular surround characteristics (*e.g.* pleural tethering)[4-6]. Hendrix *et al*[7] report that in a cohort of almost 75000 patients between 2008 and 2019 the percentage of patients with pulmonary nodules increased from 38% to 50% and the proportion of stage 1 lung cancers doubled. These findings highlight the paramount importance of correctly identifying and characterising pulmonary nodules.

The concept of low-dose CT (LDCT) chest imaging was proposed by Naidich *et al*[8] in 1990. The National Lung Screening Trial, a randomised control trial in 2011, demonstrated a 20% reduction in mortality when LDCT chest was utilised in favour of traditional chest radiography in screening an asymptomatic high risk population[9]. LDCT has been utilised for over a decade in screening programmes of high risk patients for lung malignancy and its ability to characterise solid pulmonary nodules is well established[10]. However, the use of serial ionising radiation examinations in an asymptomatic population raises concern regarding cumulative effective dose (ED) and subsequent carcinogenesis[11]. Ultra-LDCT (ULDCT) chest imaging protocols have been developed in an effort to further reduce this ionising radiation burden. Inadequate signal to noise ratio (SNR) has typically been the most common limitation of ULDCT techniques and recent advances in hardware and software in a range of clinical settings, have shown potential in surmounting this limitation. Model-based iterative reconstruction (MBIR) takes advantage of statistical algorithm techniques to model x-ray production, tissue attenuation and sources of noise in a CT examination which allows large reductions in noise in the reconstructed images[12].

ULDCT chest imaging protocols with MBIR have been shown to facilitate both a large reduction in radiation dose and produce CT images capable of providing comparable diagnostic accuracy of respiratory pathology in comparison with the more traditional filtered back projection reconstruction technique[13-15]. Maintaining diagnostic integrity is essential

when adjusting imaging protocols. The ability of ULDCT chest protocols to detect and characterise pulmonary nodules has been demonstrated in numerous *in vitro* studies[16-19]. Currently, the clinical utility of ULDCT chest in the assessment of pulmonary nodules is uncertain.

In this study, we aimed to prospectively compare ULDCT chest combined with MBIR with standard dose CT (SDCT) chest in the detection, measurement and characterisation of solid pulmonary nodules. A secondary aim was to compare the radiation dose between the two protocols.

MATERIALS AND METHODS

Study design and population

Following institutional ethical board approval (Clinical Research Ethics Committee reference number: ECM4(g)1/3/16 & ECM3(nnnn)9/3/21) a prospective cohort study was conducted. The study population consisted of adult patients (n = 30) attending respiratory outpatient clinic for surveillance of previously detected indeterminate solid pulmonary nodules on SDCT chest.

Inclusion criteria for the study were as follows: > 35 years of age, ability to provide informed written consent, and current or former smoker. Exclusion criteria were as follows: Unable to give informed consent, active malignancy, pregnancy or any condition, or ailment precluding the ability to lie flat for the duration of the scan.

Each potential participant was given information in simple language about the objective, methods, and risks of study participation. The study procedure which involved the acquisition of reference SDCT chest followed by an ULDCT chest was explained to all subjects. If aggregable to participation, written informed consent was obtained.

CT imaging technique

A SDCT and an ULDCT chest without intravenous contrast were acquired with a 64-row multi-detector CT system (Discovery CT750 HD; GE Healthcare, Waukesha, WI, United States). Our previously published MBIR ULDCT chest protocol was utilised in all ULDCT acquisitions[14]. Briefly, this involved a tube voltage: 80 Kv; tube current: 20 mA; gantry rotation time: 0.4 seconds; pitch factor: 1.375; and FOV of 32 cm. Scanning was performed at end-inspiration from lung apices to bases. No additional expiratory phase imaging was performed. Images were acquired at slice thickness of 0.625 mm.

Nodule identification, measurement and characterisation

Nodules were detected, measured and characterised, according to the Fleischner Society Guidelines, independently on review of the PACS system on a dedicated workstation (Advantage Workstation VolumeShare 2, Version 4.4, GE Medical Systems, Milwaukee, WI, United States) by two consultant radiologists with a subspeciality interest in chest radiology[4].

Objective image quality

Objective image quality analysis was performed independently on a dedicated workstation (Advantage Workstation VolumeShare 2, Version 4.4, GE Medical Systems, Milwaukee, WI, United States) by two readers in line with our previously published work[20]. The readers were blinded to the scanning protocol used and the order of the datasets was randomized. Briefly, attenuation values were measured in Hounsfield units (HU) at three levels: Aortic arch, carina, and the maximum cardiac diameter. Measurements were recorded by placing circle histograms of equal size (diameter, 10 mm) in the descending aorta and paraspinal muscles of the posterior chest wall at each level. These regions of interest (ROIs) were placed in a homogenous area, taking care to avoid fat planes and blood vessels. The standard deviation of the mean attenuation in the ROI served as an objective measure of image noise. The SNR of each ROI was calculated by dividing the mean HU by its standard deviation. Measurements were taken three times by each operator to reduce error and the mean recorded. The mean of both readers' measurements was used for analysis.

Subjective image quality

The ability to identify and characterise the pulmonary nodules on the ULDCT chest protocol was subjectively scored by two readers on a scale of 1-10, with 1 being unacceptable, 5 acceptable and 10 excellent. The ULDCT chest was also subjectively rated for overall diagnostic acceptability on the same scale. The mean of both readers' measurements was used for analysis. The subjective image quality of the ULDCT chest with MBIR was assessed independently and not directly compared with the corresponding SDCT chest for each patient. SDCT chest is our institution's 'gold standard' for the assessment of lung nodules and is considered 10/10 on subjective image quality assessment.

Radiation dose analysis

Radiation dose data were taken from individual institutional reports. The CT dose index volume ($CTDI_{vol}$) in mGy and dose length product (DLP) in mGy.cm were recorded. The ED was calculated using a conversion factor of 0.014 as per validated literature[21].

Statistical analysis

Statistical analysis was carried out using SPSS version 28 (IBM SPSS Inc., Chicago, Il). Data were exported into SPSS from Microsoft Office Excel (Microsoft Corporation, CA, United States) for statistical analysis. Descriptive statistics were utilised for patient demographics. Following Shapiro-Wilk normality testing, a paired t-test was utilised to compare the

ULDCT and SDCT protocols. Intraclass correlation coefficient (ICC) was used to evaluate interrater reliability. A P value of < 0.05 was considered statistically significant. Data are presented as median and standard deviation unless otherwise specified in the text.

RESULTS

Thirty patients (13 female; 17 male) (mean age 64 ± 12.3 years) were included. Each patient underwent both SDCT chest and ULDCT chest with MBIR examinations and these findings were compared with previously performed index imaging to establish a baseline nodule burden. The mean duration between index and follow up examinations was 217 days.

Nodule identification, measurement and characterisation

One hundred and twenty-two nodules (100 solid nodules) were detected on ULDCT chest (mean of 4.1 nodules), and 116 nodules (98 solid nodules) were detected on SDCT chest (mean of 3.9 nodules; Table 1).

The number of solid pulmonary nodules on SDCT chest in comparison with index CT were similar with the expected interval resolution and subsequent development of a small number of pulmonary nodules.

There was no significant change in size of the solid pulmonary nodules detected between ULDCT chest with MBIR and SDCT chest protocols. The mean pulmonary nodule size for ULDCT chest was 4.51 ± 2.47 mm and for SDCT chest was 4.47 ± 2.53 mm (P = 0.328; Figure 1). ICC as an indication of interrater agreement for nodule size on ULDCT was r = 0.961 and on SDCT, r = 0.933 (excellent reliability).

There was no significant difference in the characteristics of correctly identified nodules when comparing SDCT chest to ULDCT chest with MBIR protocols (P = 0.09). For example, there was no significant difference in the ability to characterise lesions as cavitating or spiculated (Figure 2).

The ULDCT chest protocol demonstrated a small number of false positive and false negative pulmonary nodules when compared to the traditional SDCT chest protocol (Figure 3 and Figure 4 respectively). These minor discrepancies did not reach statistical significance.

Objective image quality

Objective noise and SNR were measured in the aortic lumen and paraspinal muscles at the level of the aortic arch, carina and largest cardiac diameter (Table 2). Noise was significantly reduced in the paraspinal muscles at the level of the aortic arch and carina in the ULDCT chest protocol (reconstructed with MBIR) in comparison with the SDCT chest protocol (P < 0.001). SNR was significantly increased in the ULDCT chest with MBIR in comparison to SDCT chest in all areas except in the paraspinal muscle at the maximum cardiac diameter level (P < 0.001). The remainder of the results did not reach statistical significance.

Subjective image quality

The mean subjective image quality score, from a maximum score of 10, for the ability to identify and characterise the pulmonary nodules on ULDCT with MBIR was 7.8 ± 1.48 and overall diagnostic acceptability was 8.9 ± 0.93. The ICC for diagnostic satisfaction had an r value of 0.548 and quality of nodule visualisation r value was 0.511 (moderate reliability).

Radiation dose analysis

The mean DLP, $CTDI_{vol}$ and ED for the ULDCT chest with MBIR protocol were 5.592 mGy.cm, 0.16 mGy and 0.08 mSv respectively. These were significantly less than the SDCT chest protocol with mean DLP, $CTDI_{vol}$ and ED of 237.1 mGy.cm, 7.2 mGy and 3.21 mSv respectively (P < 0.001). This represents an overall radiation dose reduction of 97.6%.

DISCUSSION

This prospective cohort study demonstrates that ULDCT chest combined with MBIR is adequate when compared to SDCT chest in the identification, measurement and characterisation of previously identified solid pulmonary nodules while facilitating a 97.6% associated reduction in radiation dose (mean ED of 0.08 mSv *vs* 3.21 mSv).

Excessively long computer processing times is a typical limitation of advanced reconstruction algorithms and MBIR represents the latest attempt to overcome this and facilitate its routine inclusion in clinical practice[22]. A clear benefit of CT radiation dose reduction techniques are the potential benefits in paediatric patient cohorts in particular. MBIR has been shown to be superior to other reconstruction techniques in imaging children[23,24]. Carcinogenesis risk due to lifetime cumulative ED from medical imaging is a challenging topic without a definitive consensus. A large systematic review and dose-response meta-analysis assessing over 110 million adults over 3 continents found an inordinate increase in cancer risk in adults that positively correlated with CT radiation dose exposure[25]. Given the current data, a prudent approach is one that endeavours to reduce the radiation dose delivered to the patient without compromising diagnostic integrity. In concordance with other published work, our MBIR protocol facilitated a large reduction in radiation dose while maintaining diagnostic integrity[26].

With such a large reduction in radiation dose there are inevitable concerns regarding the potential consequences of misdiagnosis. In our prospective study of 30 patients, the ULDCT chest with MBIR protocol identified slightly more solid pulmonary nodules than the SDCT chest protocol (100 *vs* 98 solid pulmonary nodules respectively). When considering

Table 1 Comparison of nodule identification

Identified nodules	Index SDCT	Study SDCT	ULDCT
Solid nodules	94	98	100
Ground glass opacities	5	4	5
Calcified granulomas	10	11	14
Part solid nodules	4	3	3
Total	113	116	122

Comparison of nodule identification between the index standard dose computed tomography (SDCT), study SDCT and ultra-low dose computed tomography (ULDCT) chest imaging protocols. This table demonstrates minimal variability between protocols with ULDCT identifying slightly more solid pulmonary nodules than the SDCT. This discrepancy did not reach statistical significance. SDCT: Standard dose computed tomography; ULDCT: Ultra-low dose computed tomography.

Table 2 Noise and signal-to-noise ratio

Level	10 mm ROI	Noise (HU)			SNR		
		ULDCT	SDCT	*P* value	ULDCT	SDCT	*P* value
Aortic arch	Aortic lumen	22.28 ± 3.6	21.06 ± 2.9	0.149	2.86 ± 0.8	1.53 ± 0.3	**< 0.001**
	Paraspinal muscles	20.86 ± 3.6	27.29 ± 4	**< 0.001**	2.84 ± 0.7	1.89 ± 0.4	**< 0.001**
Carina	Aortic lumen	23.8 ± 12.4	22.98 ± 4.2	0.359	2.63 ± 0.9	1.57 ± 0.6	**< 0.001**
	Paraspinal muscles	22.33 ± 4.4	28.28 ± 4.9	**< 0.001**	2.35 ± 1.1	1.72 ± 0.5	**< 0.001**
Max. cardiac diameter	Aortic lumen	23.14 ± 7.9	27.7 ± 12.9	0.061	2.14 ± 0.9	1.17 ± 0.6	**< 0.001**
	Paraspinal muscles	23.44 ± 3.2	23.37 ± 4	0.472	1.66 ± 0.6	1.61 ± 0.6	0.318

Bold face *P* value indicates statistical significance.

Comparison of objective quantitative measures of image noise and signal-to-noise ratio at three levels from the ultra-low dose computed tomography (ULDCT) with model-based iterative reconstruction and standard dose computed tomography chest protocols. Overall, there is a statistically significant increase in signal to noise ratio in the ULDCT imaging protocol. HU: Hounsfield units, SNR: Signal to noise ratio; ROI: Region of interest; ULDCT: Ultra-low dose computed tomography; SDCT: Standard dose computed tomography.

inherent false positive and false negative results in any diagnostic test and interobserver variability, this slight discrepancy is not unexpected. Interobserver variability in identifying pulmonary nodules is well documented and we have demonstrated no statistically significant difference between ULDCT with MBIR and SDCT chest[27].

Gheysens *et al*[28] report that in a prospective study of 63 patients, a scoutless fixed-dose ULDCT chest was comparable to SDCT chest in detection of pulmonary nodules > 50 mm^3 in size, the volume variation in the assessed nodules was within previously reported interscan variability, and body habitus did not affect nodule detection. However, LDCT chest has been shown to underestimate the size/volume of smaller pulmonary nodules, which is an area of continued attention in this rapidly progressing field[17]. Dunning *et al*[29] have shown the utilisation of an ultra-sharp kernel in a modern photon-counting detector LDCT chest examination in various phantoms increases the accuracy of pulmonary nodule measurement.

In a study of 99 patients, Miller *et al*[30] assessed the reliability of ULDCT chest in identifying pulmonary nodules in comparison to a reference LDCT chest and, in line with our study, found excellent sensitivity and specificity with a significant radiation dose reduction. Paks *et al*[31] have shown ULDCT chest to be comparable to SDCT chest for solid pulmonary nodules > 2 mm in a prospective 57 patient cohort and propose its utilisation in serial imaging of known pulmonary nodules. Multiple groups have prospectively compared ULDCT chest with LDCT or SDCT chest and concluded adequate image quality and sensitivity in nodule detection[32-35].

These findings highlight the value of continued *in vitro* and *in vivo* research in ultra-low dose CT imaging and represent encouraging progress in the field.

Objective image quality was improved in our ULDCT chest with MBIR protocol with increased SNR in almost all assessed areas, substantiating recent advances in hardware and software and in particular the power of MBIR. MBIR is particularly useful in thoracic imaging given the high inherent contrast between background normal lung parenchyma and solid pulmonary nodules[36]. Iterative reconstruction methods produce less image noise than traditional filtered back projection methods[37]. Subjective image quality was more than acceptable in our study in terms of nodule identification (mean score 7.8/10) and diagnostic acceptability (mean score 8.9/10) for both readers. The ability for diagnostic radiologists to trust the objective and subjective image quality of ULDCT is essential for ongoing advancements in the

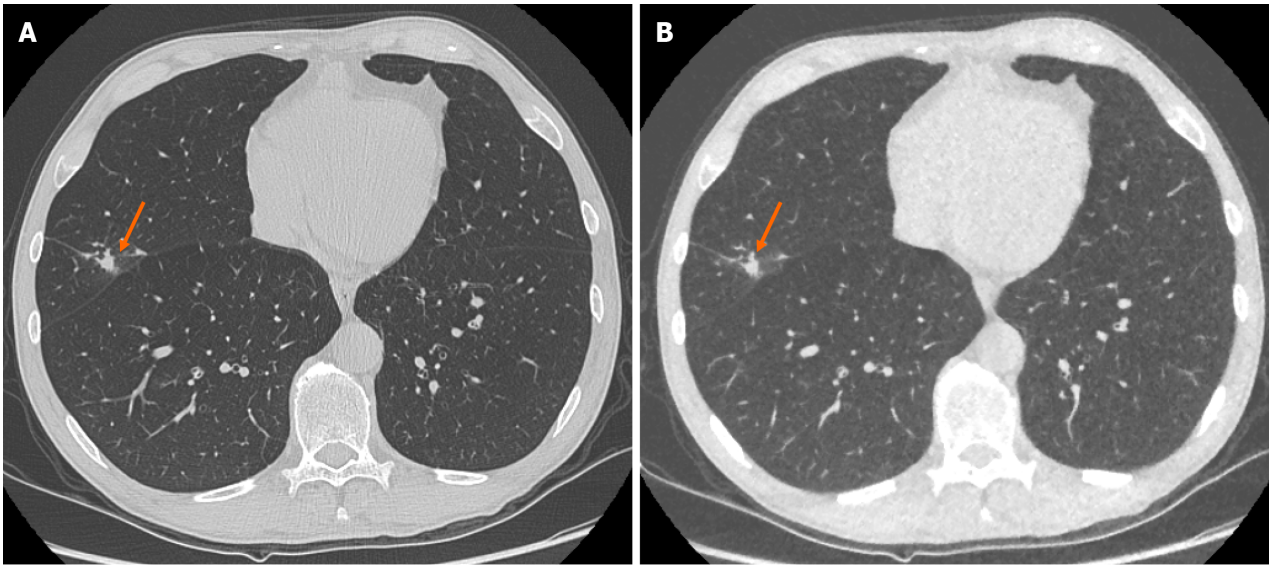

Figure 1 Representative images demonstrating image quality and ability to identify pulmonary nodules on both standard dose computed tomography chest and ultra-low-dose computed tomography chest with model-based iterative reconstruction imaging protocols. A: Selected axial slice of a standard dose computed tomography (CT) chest presented in lung windows with a solid pulmonary nodule with spiculation and pleural tethering in the lateral segment of the middle lobe (arrow); B: Selected axial slice of an ultra-low dose CT chest in the same patient at the same level presented in lung windows with the same correctly identified pulmonary nodule in the middle lobe (arrow). These images demonstrate the ability of ultra-low-dose CT chest with model-based iterative reconstruction to adequately maintain diagnostic accuracy with regard to solid pulmonary nodules.

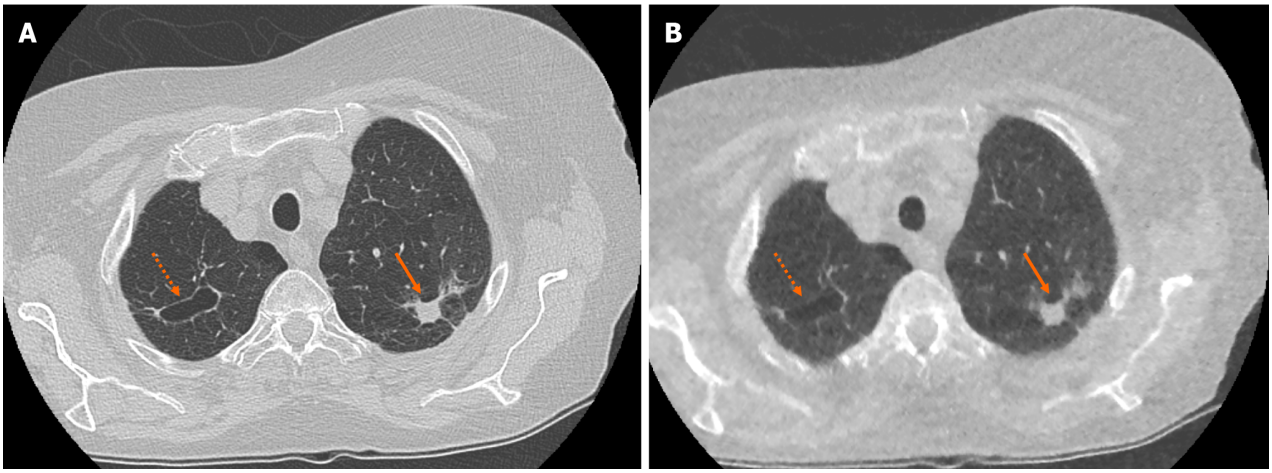

Figure 2 Example of accurate pulmonary nodule characterisation on ultra-low-dose computed tomography chest. A: Selected axial slice of a standard dose computed tomography (CT) chest presented in lung windows with a spiculated solid pulmonary nodule with pleural tethering in the apico-posterior segment of the left upper lobe (solid arrow) and a parenchymal cyst in the apical segment of the right upper lobe (dashed arrow); B: Selected axial slice in the same patient presented in lung windows at the same level highlights the ability of ultra-low-dose CT chest with model-based iterative reconstruction to correctly characterise pulmonary nodule features such as spiculation, tethering and cavitation.

field.

Reduction or elimination of common CT related image artifacts becomes increasingly relevant in ULDCT with the inevitable reduction in signal as a consequence of the reduced radiation dose. Recent phantom work by Watanabe *et al* [38] has shown the addition of a dedicated tin filter photon shield reduced pacemaker related artefact in ULDCT and subsequently improved pulmonary nodule detectability. The ability of clinical imaging to diagnose patients at ever reducing radiation doses with adequate image quality is heavily supported by phantom and other non-clinical research which facilitates ongoing meaningful advances in imaging technique development.

The exciting new field of advanced image analysis through radiomics and deep learning algorithms has the potential to improve nodule characterisation and subsequent patient prognostication. Automatic nodule detection software in various forms have been utilised in ULDCT nodule detection and characterisation to good effect[26,39]. The limitations of heterogeneity in image acquisition, accurate data segmentation, limited reproducibility of results across different radiomics platforms and the novelty of the field have prevented advanced imaging analysis being utilised routinely in current daily practice[40].

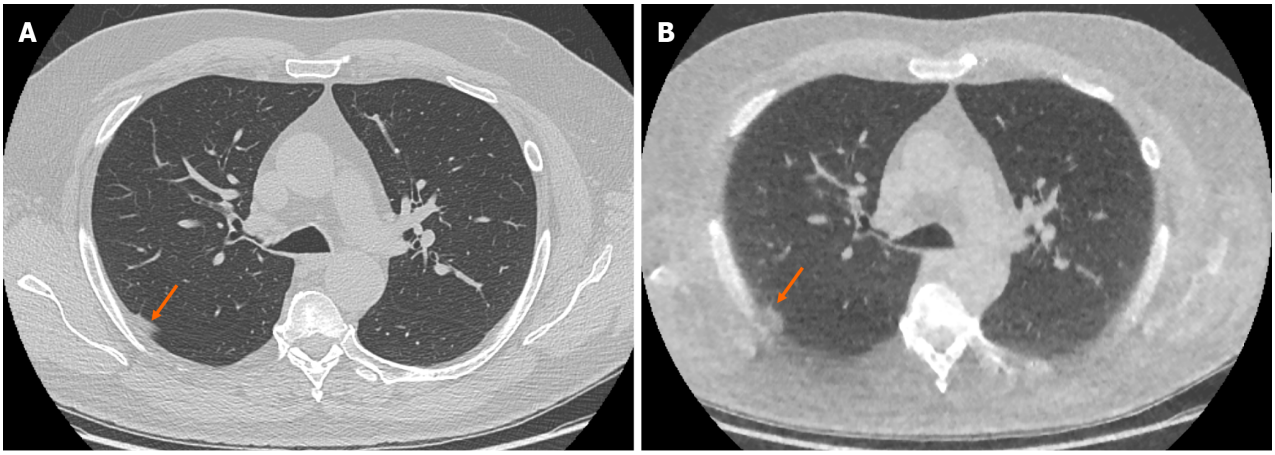

Figure 3 Example of false positive pulmonary nodule identification on ultra-low-dose computed tomography chest. A: Selected axial slice of a standard dose computed tomography (CT) chest presented in lung windows with a small focus of peripheral atelectasis in the posterior segment of the right upper lobe (arrow); B: Selected axial slice of an ultra-low dose CT chest with model-based iterative reconstruction presented in lung windows at the same level in the same patient with the focus of soft tissue attenuation in the posterior segment of the right upper lobe incorrectly identified as a solid pulmonary nodule (arrow). The incidence of false positive solid nodule identification was minimal and did not reach statistical significance.

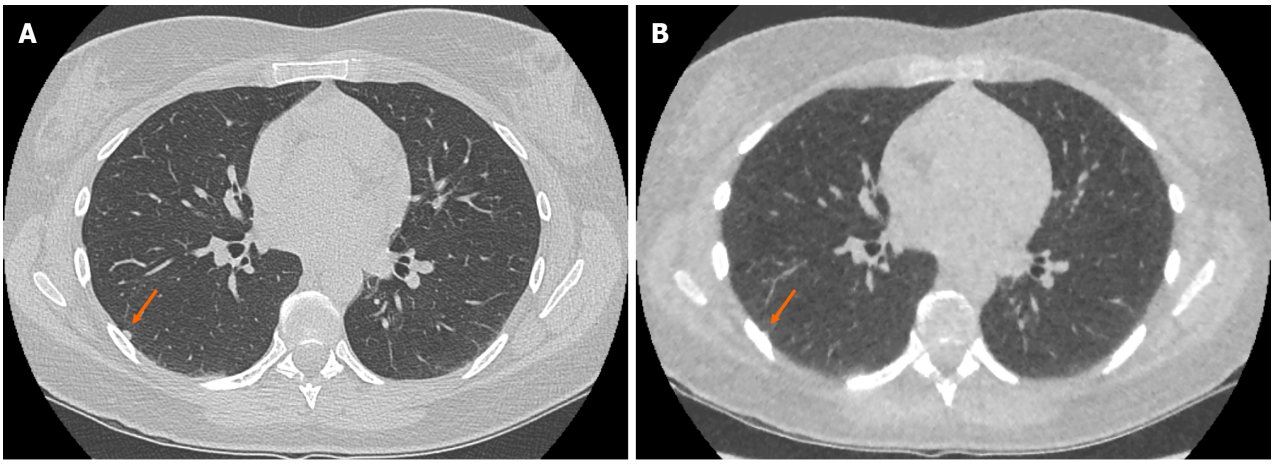

Figure 4 Example of false negative pulmonary nodule identification on ultra-low-dose computed tomography chest. A: Selected axial slice of a standard dose computed tomography (CT) chest presented in lung windows with a solid pulmonary nodule abutting the pleura in the lateral segment of the right lower lobe (arrow); B: Selected axial slice of an ultra-low dose CT chest with model-based iterative reconstruction in the same patient at the same level presented in lung windows demonstrating the less conspicuous pulmonary nodule that was not identified (arrow). The incidence of false negative solid nodule identification was minimal and did not reach statistical significance.

This study had several limitations including its limited sample size of data from a single centre. Volumetric analysis is not routinely performed in our institution and therefore did not form a part of this study. However, the ability of MBIR to facilitate accurate volumetric analysis has been shown in a phantom study by Chen *et al*[41]. Our study did not assess the upfront identification of pulmonary nodules with ULDCT in patients without documented prior nodules or any change in pulmonary nodules over time.

CONCLUSION

ULDCT chest combined with MBIR is non-inferior to SDCT chest in the identification, measurement and characterisation of previously identified solid pulmonary nodules and facilitates a reduction in radiation dose of up to 97.6%. We propose the use of ULDCT chest in the routine follow-up of previously identified indeterminate solid pulmonary nodules.

FOOTNOTES

Author contributions: Maher MM and Henry M designed the research study; O'Regan PW, Harrold-Barry A, O'Mahony AT, Crowley C, Joyce S, Moore N, O'Connor OJ and Ryan DJ collected and assembled the data; O'Regan PW, Harrold-Barry A and O'Mahony AT

analysed the data and wrote the manuscript; Ryan DJ, Henry M and Maher MM supervised the study; all authors have read and agreed to the published version of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Clinical Research and Ethics Committee Institutional Review Board (Approval No.ECM4(g)1/3/16 & ECM3(nnnn)9/3/21).

Clinical trial registration statement: This small prospective trial was registered with the local ethics institutional review board. Original approval PDF attached. It was not required to register the study with another governing body (*i.e.* an additional Clinical Trial Registration Statement is not applicable).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declare no conflict of interest.

Data sharing statement: The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

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