



Latest CT technologies in lung cancer screening: protocols and radiation dose reduction

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Abstract: The aim of this review is to provide clinicians and technicians with an overview of the development of CT protocols in lung cancer screening. CT protocols have evolved from pre-fixed settings in early lung cancer screening studies starting in 2004 towards automatic optimized settings in current international guidelines. The acquisition protocols of large lung cancer screening studies and guidelines are summarized. Radiation dose may vary considerably between CT protocols, but has reduced gradually over the years. Ultra-low dose acquisition can be achieved by applying latest dose reduction techniques. The use of low tube current or tin-filter in combination with iterative reconstruction allow to reduce the radiation dose to a submillisievert level. However, one should be cautious in reducing the radiation dose to ultra-low dose settings since performed studies lacked generalizability. Continuous efforts are made by international radiology organizations to streamline the CT data acquisition and image quality assurance and to keep track of new developments in CT lung cancer screening. Examples like computer-aided diagnosis and radiomic feature extraction are discussed and current limitations are outlined. Deep learning-based solutions in post-processing of CT images are provided. Finally, future perspectives and recommendations are provided for lung cancer screening CT protocols.

Keywords: Lung cancer; computed tomography; screening; radiation dose reduction

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Introduction

A growing number of countries is implementing lung cancer screening programs or are at the forefront of starting with research implementation studies (1-7). The National Lung Screening trial (NLST, USA) and the Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) trial have shown that lung cancer mortality can be reduced with at least 20% with lung cancer CT screening in high risk individuals meeting eligibility criteria (8,9). Current lung cancer screening protocols recommend repeated screening at either annual or biannual frequency for eligible

individuals (10,11). On an individual level this may result in over 25 scans over a lifetime with in practice widely varying cumulative radiation dose (12,13). Consequently, the estimates for induced cancer risk by repeated screening for an entire population vary as well depending on the used CT protocol, CT generation and expertise of institutions to optimize CT protocols (12-15). The aim of this review is to provide clinicians with an overview of the development of the CT protocol for lung cancer screening, the current protocol recommendations and radiation dose reduction possibilities in lung cancer CT screening.

CT protocol settings of large lung cancer screening studies

A variety of CT systems and low dose CT acquisition protocols have been used in large lung cancer screening studies, see *Table 1*. The majority of studies were initiated before 2010, and therefore, the protocol settings (radiation dose and image quality) dates back to systems and standards of ten until twenty years ago. Lung cancer CT screening studies before 2004 used single slice detector systems or the first multi(slice)-detector systems that could acquire 4 slices per rotation, and used collimation of 2.5–5.0 mm (16–18). From the start, a spiral scan mode was used to cover the entire chest from lung apices to lung base within one end-inspiratory breath hold. Starting from studies initiated in 2004, 16-slice multi-detector CT systems were mainly used in lung cancer screening from then on. This allowed acquiring 16 slices with collimation of 0.75 mm resulting in thinner axial slices (19,23,24). From 2007 onwards, number of slices in MDCT increased to 128 with collimation as low as 0.625 mm, and scan times ranging from 5 to 10 seconds (26,27).

The tube voltage used in the major screening studies varied between 80 and 140 kVp. In general, either one fixed tube voltage and/or tube current value was applied on each CT system for every participant or pre-defined values were applied based on a participant's body weight. For instance, a low tube voltage of 80 kVp was used in slim or small participants (up to 50 kg), moderate tube voltage of 120 kVp in medium size participants (between 50–80 kg) and a high tube voltage of 140 kVp in large or tall participants (over 80 kg). Similarly, the tube current was mainly fixed at a low current of maximum 40 mA to achieve a low dose chest CT, or the tube current was adjusted in small, medium and large participants to reach predefined total radiation dose as estimated by the volume CT dose index ($CTDI_{vol}$) in mGy (23). As far as results on total mean radiation dose have been published, overall the radiation dose of the low-dose chest protocols varied between 0.8 to 1.5 mSv for medium size participants in the trials initiated between 2001 and 2011 (17,20,21,25,26). To put into context, the radiation dose of conventional high resolution CT of the chest used for clinically indicated scans, could be as high as 5.8 mSv at that time (28).

The specific reconstruction values of the various study protocols are scarcely published. Information on used field-of-view, reconstruction algorithm or window settings are not published. In general, filtered back projection (FBP)

was used to reconstruct the images at a thin slice thickness and a small increment. This resulted in overlapping slice reconstructions to increase the image quality without the need of increasing radiation dose, to acquire thin slices for the detection of small lung nodules. In the process of reconstructing the image with FBP, a convolution filter or 'kernel' is used to enhance or optimize the reconstructed image for specific anatomical areas. In the lung cancer screening studies, a 'soft' kernel and 'hard' or 'sharp' kernel was applied. See *Figure 1* for example of soft versus sharp kernel CT image. Soft kernels are optimized for visualizing soft tissues, appear as more smooth images with less noise, and are used to detect nodules and evaluate nodule morphology. Sharper kernels are suitable for visualizing high differences in density (lung-air, bone-soft tissue) structures, appear as sharp images with higher spatial resolution at the expense of higher noise, and can be used for nodule size measurements although segmentation problems may occur. A soft kernel tends to show higher reproducibility for nodule volume measurements but may underestimate nodule volume. There is no consensus yet for the use of soft or sharp kernel (22,29), in general, a medium-smooth to medium-sharp kernel is advised (30). It is of particular importance to consistently use the same reconstruction kernel in case of nodule measurements on subsequent CT scans.

International guidelines and recommendations

Several international radiology societies have published guidelines on the CT requirements for lung cancer screening, see *Table 2*, whereas the guidelines of thoracic societies mainly focus on the analysis of the CT images and lung nodule management.

The American College of Radiology (ACR), Society of Thoracic Radiology (STR) and the European Society of Thoracic Imaging (ESTI) have published practice guidelines and technical standards to assist radiologists and medical physicists in developing local CT lung cancer screening protocols (31–33). The ACR recommends using at least 16-slice MDCT, whereas the ESTI sets the lower limit at 32-slice and recommends 64-slice MDCT. The total scan time is recommended to be below 10 seconds to cover the total chest within a single breathhold. A tube voltage of 100–120 kVp is acceptable for standard sized patients, whereas a tube voltage of 140 kVp may be used in obese patients. The tube current should be set in conjunction with the tube voltage and pitch to meet certain $CTDI_{vol}$.

Table 1 CT acquisition protocol large lung cancer screening studies

Author	Study, n*, start year	CT System	Tube voltage (kVp)	Tube current (mA)	Scan mode (pitch)	Collimation	Kernel	Slice thickness/increment	Mean radiation dose
Infante <i>et al.</i> 2008 (16)	DANTE, n=1,276, 2001	SDCT	140 kVp	40 mA	Spiral	1×5 mm	Bone kernel	~5 mm	–
National lung screening trial research team 2011 (17)	NLST, n=26,722, 2002	4 (or higher) MDCT	120–140 kVp	20–30 mAs/pitch; 40–80 mAs	Spiral	<2.5 mm	Soft (tissue) kernel	1.0/1.0 mm; 3.2/2.5 mm	1.5 mSv (estimated)
Lopes Pegna <i>et al.</i> 2009 (18)	ITALUNG, n=1,613, 2004	SDCT; MDCT	120 kVp; 140 kVp	20 mA; 43 mA	Spiral	–	Bone kernel	3.0/3.0 mm; 1.0/1.0 mm; 1.5/1.5 mm	–
Pedersen <i>et al.</i> 2009 (19)	DEST, n=2,052, 2004	16 MDCT MX8000, Philips	120 kVp	40 mAs	Spiral (1.5) 0.5 s rot	16×0.75 mm	'soft' and 'hard' kernel	3.0/1.5 mm and 1.0/1.0 mm	–
van Klaveren <i>et al.</i> 2009 (20); Xu <i>et al.</i> 2006 (21); Wang <i>et al.</i> 2010 (22); Zhao <i>et al.</i> 2011 (23)	NELSON, n=7,557, 2004	16 MDCT; Sensation 16, Siemens; Brilliance 16p/ MX8000 IDT, Philips	80–90 kVp (<50 kg); 120 kVp (50–80 kg); 140 kVp (>80 kg)	CTDI dependent to reach preset fixed dose.	Spiral (1.3)	16×0.75 mm	Soft (B30) kernel; Sharp (B60) bone kernel Siemens	1.0/0.7 mm	CTDIvol (mGy): 0.8; 1.6; 3.2
Pastorino <i>et al.</i> 2012 (24)	MILD, n=2,376, 2005	16 MDCT, Somatom Sensation, Siemens	120 kVp	30 mAs	Spiral (1.5); 0.5 s rot	16×0.75 mm	Sharp: B50, Siemens	1.0/1.0 mm	–
Becker <i>et al.</i> 2012 (25)	LUSI, n=2,029, 2007	16 MDCT Toshiba 128 MDCT Siemens	–	–	–	–	–	1.0/0.7 mm; 1.0/0.8 mm	1.6–2.0 mSv
Baldwin <i>et al.</i> 2011 (26); Field <i>et al.</i> 2016 (27)	UKLS, n=1,994, 2011	16 (or higher) MDCT 128 Definition, Siemens; 64 Brilliance, Philips	90 kVp (<50 kg); 120 kVp (50–80 kg); 140 kVp (>80 kg)	CTDI dependent to reach preset fixed dose	Spiral (0.9–1.1)	MDx 0.5–0.625 mm	Moderate kernel	1.0/0.7 mm	0.8 mGy (0.4 mSv); 1.6 mGy (0.8 mSv); 3.2 mGy (1.6 mSv)

*, number of participants that underwent CT screening. CTDIvol, CT dose index volume; MDCT, multi detector CT; SDCT, single row CT.

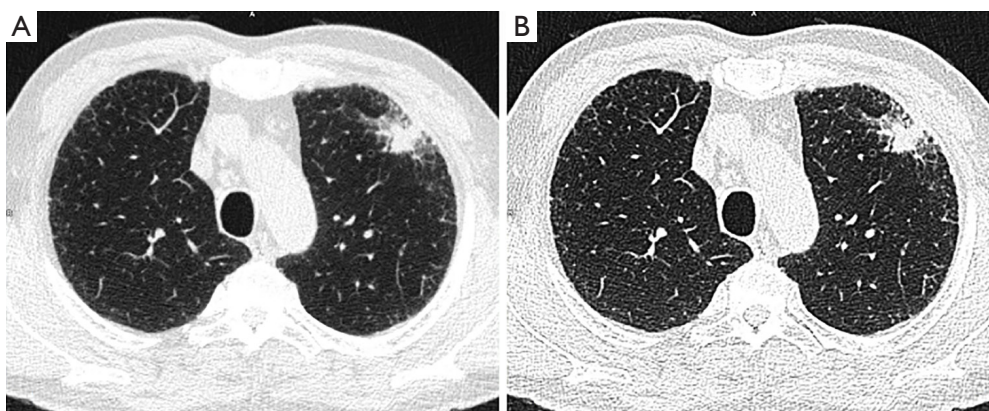


Figure 1 Example of low dose CT protocol with 120 kVp and FBP reconstructed with (A) soft and (B) hard kernel in a patient presenting with an irregular solid nodule of 3,973 mm³ (maximum diameter 26.7 mm) in the left upper lobe.

Beam-hardening pre-filters like tin-filter (Sn) may be applied if available on the CT system (33). The guidelines discourage the use of fixed tube currents, but highly recommend the use of automated tube current modulation based on a patient's habitus. Moreover, the use of automated tube voltage selection and organ dose modulation is advised. The ACR recommends a pitch between 0.7–1.5, but states that this parameter should be set with the other acquisition parameters mentioned before and the $CTDI_{vol}$. This pitch factor is inherent to the system settings since it is based on the rotation time, table feed and output (beam width) of a CT system. The $CTDI_{vol}$ to be met decreased over the years, the ACR in 2014 reports a level of <3 mGy for standard patient size, while the ESTI 2019 reports levels of <1.6 mGy for patient size >80 kg, resulting in an effective radiation dose of approximately 0.7 mSv.

In contrast to the former studies, the current guidelines report in detail on the reconstruction parameters to be used. Reconstruction of the CT images is preferred at slice thickness ≤ 1.0 mm and a slice increment smaller than the slice thickness (≤ 0.7 mm), but overlapping reconstructions are not mandatory. The field-of-view may be optimized for every patient to include the entire lungs up to 1 cm beyond the rib cage. Standard body or mediastinum/soft tissue and lung kernels should be used and additionally a medium-sharp (lung) kernel without edge enhancement may be used. Moreover, during analysis it is advised to use maximum intensity projections (MIP) and multiplanar reconstruction (MPR) for lung nodule detection and nodule characterization respectively, see *Figure 2*. Both guidelines strongly recommend the use of iterative reconstruction or deep learning reconstruction to allow further dose

reduction while maintaining image quality. The ESTI guideline discourages the use of FBP (33).

In addition to the radiological societies, a working group of the American Association of Physicists in Medicine (AAPM) developed a set of detailed acquisition protocols of over 30 CT systems of six major vendors for lung cancer screening purposes (34). These protocols are based on the experience gained with the NLST study and other screening studies by the working group. Similar to the ACR guideline, these protocols should result in radiation dose ($CTDI_{vol}$) ≤ 3 mGy (≤ 1.0 mSv) for a standardized patient of 70 kg. However, radiation dose may vary from 0.25 to 5.6 mGy for patient of 50 to 120 kg.

Other societies provide limited information on CT protocol requirements, but they highlight the importance of using thin slices (< 1.25 mm) and MPR, or MIP for the detection and quantification and characterization of lung nodules and using a low dose technique (11,35–37). Specifically, the Fleischner Society addresses that small nodules (< 10 mm in diameter) should be quantified on sharp (high spatial resolution) kernel while in larger nodules (> 10 mm) the reconstruction kernel has less impact on measurement accuracy (38).

Radiation dose reduction

In the past 5 years, multiple studies have evaluated the impact of lowering the radiation further from LDCT to ultra-low dose CT (ULDCT) with submillisievert dose level. Common applied dose reduction techniques are reducing the tube output by decreasing the tube current and/or tube voltage or by using beam filtration with a tin-

Table 2 International radiological society's CT protocol guidelines

	ACR – STR [Kazerooni <i>et al.</i> 2019 (31); ACR 2014 (32)]	ESTI [Revel <i>et al.</i> ESTI 2019 (33)]
CT system type	≥16 MDCT	≥32 MDCT, ≥64 preferred
Rotation time	≤750 ms	≤500 ms
Pitch	0.7–1.5*	As suggested by vendors*
Scan duration	Scan time <15 s (single breathhold)	≤10 s (shorter preferred, single breath hold)
Scan mode	Spiral	Spiral
Tube voltage	100 to 140 kVp* for standard sized patient	100 to 120 kVp for standard sized patient 140 kVp for obese participant
	kVp should be set in combination with mAs to meet CTDI _{vol} specifications	Preferably reduce mAs first and then kVp If available: beam-hardening pre-filtering with Sn filter is strongly advised
Tube current	Not specified*	No fixed mAs setting unless at very low dose
Dose modulation	If available use: automatic tube current modulation, automated kVp selection; if not available: use manual adjusted settings based on patient body habitus and age	If available use: automatic tube current modulation, automated kVp selection, organ dose modulation
Radiation dose (CTDI _{vol})	≤3 mGy for standard patient	Depending on participant weight: <50 kg: 0.4 mGy; 50–80 kg: 0.8 mGy; >80 kg: 1.6 mGy
FOV	Optimized for each patient: 1-cm beyond rib cage; does not need to include entire chest wall thickness	Does not need to include entire chest wall thickness
Slice thickness	≤2.5 mm slice thickness, ≤1.0 mm preferred	≤1.0 mm, ≤0.75 mm preferred, 1.25 mm may be necessary in obese patients
Slice increment	≤ slice thickness Overlapping reconstructions not mandatory	≤ slice thickness, maximum 0.7 mm Overlapping reconstructions not mandatory
Reconstruction algorithm	Consistent with diagnostic CT studies; IR algorithms encouraged	IR or deep learning reconstruction; use of FBP reconstruction algorithms is strongly discouraged
Reconstruction kernel	Standard (mediastinum and lung); additional high spatial frequency (lung parenchyma) is optional	Standard body kernel; additional lung kernel is optional

* should be set with other technical parameters to achieve CTDI_{vol} specifications. ACR-STR, American College of Radiology-Society of Thoracic Radiology; ESTI, European Society of Thoracic Imaging; FBP, filtered-back projection; FOV, field of view; IR, iterative reconstruction; MDCT, multi-detector computed tomography; MIP, maximum intensity projections; MPR, multi-planar reconstruction.

filter. Reduction of the output would lead to decreased image quality and therefore these techniques are often applied in a protocol with iterative reconstruction.

Decreasing tube current and iterative reconstruction

In the dose reduction studies, the reference LDCT protocols, CT systems and iterative reconstruction algorithms differ considerably (39-44). In the study of Lim *et al.* a high-pitch scan mode with iterative reconstruction at 120 kVp with fixed tube current of 30 mAs resulted in 34% dose reduction (2.1 *vs.* 3.1 mGy) with similar image quality

and reduced cardiac motion artifacts compared to reference low-dose chest CT at 120 kVp with FBP and low pitch (44). Nevertheless, a fixed tube current of 30 mAs was used in 30 healthy volunteers and reconstructions were made at 3.0/3.0 slice thickness and increment, making the study set-up less suitable to determine the impact on lung nodule evaluation.

In a study of Ye *et al.* the authors specifically investigated the sensitivity for nodule detection of an ULDCT protocol compared to LDCT protocol in 188 individuals (39). The ULDCT was performed at 120 kVp with 10 mA while the LDCT was executed at 120 kVp with 50 mA. In both protocols IR 50% [adaptive statistical iterative

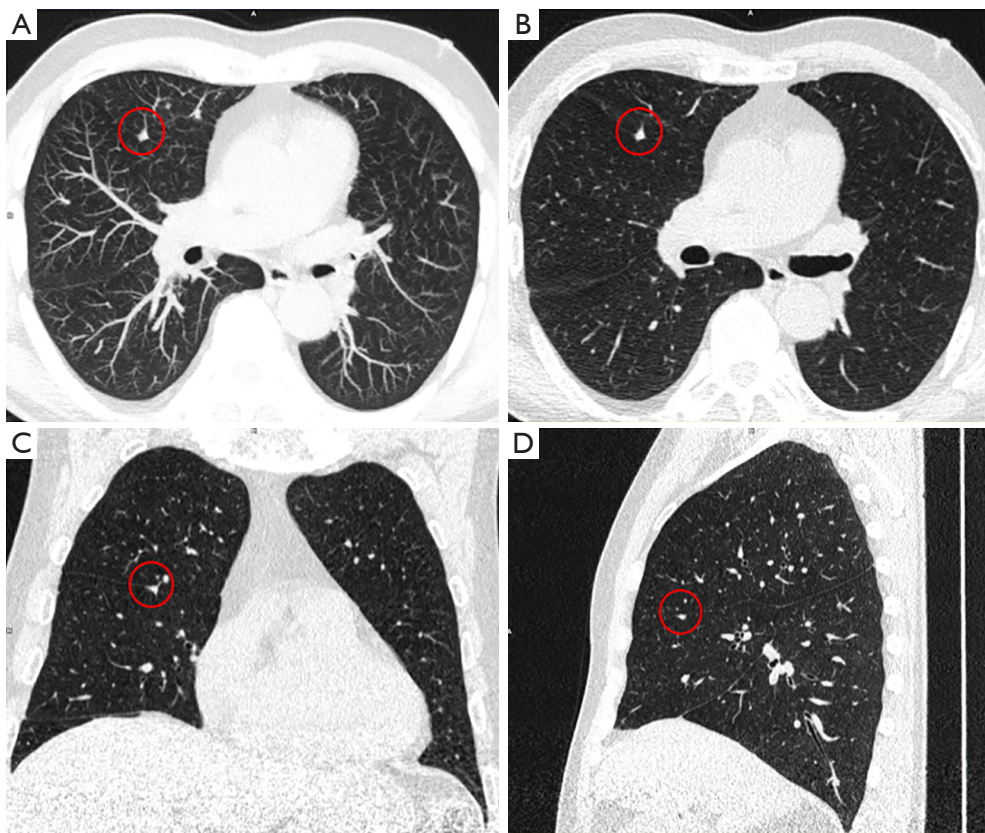


Figure 2 Example of the use of (A) maximum intensity projection (MIP, thickness 10 mm) and (B,C,D) multiplanar reconstructions (MPR, thickness) for lung nodule detection and nodule characterization in a patient presenting with a perifissural nodule (highlighted in red circle) of 80 mm³ in the right middle lobe.

reconstruction V (ASiR-V)] was applied, and images were reconstructed at slice thickness and increment of 2.5 mm. The authors found that nodule type (solid, sub-solid) and nodule size (diameter) had influence on the sensitivity. For example, the sensitivity for nodule detection was overall 90.4% while this could be increased to 98.2% if only nodules with diameter of ≥ 6 mm were considered. Although the dose could be reduced from 0.93 to 0.096 mSv based on ULDC, images were reconstructed at relatively thick slice thickness. Reducing the slice thickness to the preferred 1.0 mm may drastically impede image quality and sensitivity for nodule detection. Nevertheless, in a study of Zhang *et al.* ULDC protocols with IR [iterative model reconstruction (IMR)] and with thin slices were used (1.0 mm). This study showed that the use of ULDC with IMR resulted in similar nodule detectability as the reference LDCT with FBP and with hybrid IR, while diagnostic image quality for lung and mediastinum was preserved. However, the ULDC protocol in this study was with

0.67 mSv considerably higher than the former study, while obese patients were excluded (42).

Tin-filter and iterative reconstruction

Several CT systems from one vendor are equipped with a tin filter than can be applied to block the low-energy part of the X-ray spectrum. This part of the spectrum would otherwise have been absorbed by the patient's body and would not have contributed to the image quality but would have increased the total radiation dose.

In a phantom study from Martini *et al.* the sensitivity of a low-dose tin filter protocol combined with IR [advanced modeled iterative reconstruction (ADMIRE) level 5] for solid and sub-solid nodule detection was determined (45). Sensitivity was 100% and 93.8% for solid and sub-solid nodules ranging in size from 2–10 mm at dose of 0.10 mGy. With a slightly higher dose (0.30 mGy), by increasing the tube current from 30 to 80 mAs, also a sensitivity of

100% for sub-solid nodules could be reached. In addition, in a phantom study of Eberhard *et al.* the impact of low dose tin filter protocol on volume measurements of solid nodules was determined. This study showed similar results for standard dose CT and the tin filter protocol for nodule volume ranging from 34–524 mm³ (diameter 4–10) (46). However, absolute percentage error increased for images reconstructed with higher levels of IR (ADMIRE 3 and 5) compared to FBP. This may affect calculation of volume doubling times and consequently impact the clinical management. Nonetheless, volume measurement of solid nodules may still be reliably performed by using a Sn100kVp protocol with FBP at CTDI_{vol} of 0.10 mGy.

In a patient study of Messerli *et al.* an almost similar CT protocol was applied as in the phantom study of Martini *et al.*, namely Sn100kVp with IR (ADMIRE level 3) at 70 mAs (47). The ultra low-dose Sn protocol was applied in 202 patients and sensitivity and image quality were compared to the full dose protocol with 110 kVp and IR (ADMIRE level 3). This patient study showed slightly lower sensitivity of 97.3% and 92.6% for all nodules types and sub-solid nodules of >5 mm, respectively, compared to the phantom study. However, the majority of false negative nodules on ultra low-dose scans had diameter of ≤2.0 mm on the full dose scan, which is well below the lowest size threshold in nodule management protocols. Although the image quality was significantly lower in the ultralow dose protocol this seemed not to affect the detection of relevant lung nodules. Therefore, the radiation dose could be reduced from 3.9 to 0.3 mGy by applying tin-filter protocol with IR. Nonetheless, the impact of the ultralow dose protocol on diameter or volume measurement error was not evaluated in this patient study.

To conclude, the radiation dose may be further decreased beyond the currently recommended guidelines, by using iterative reconstruction and a low tube current or tin-filter. However, the majority of studies investigated only the impact on nodule detection based on certain diameter size with cut-off values varying between studies. Also, only a few studies specified sensitivity by nodule type and many studies excluded obese patients. Therefore, one should be cautious in reducing the radiation to ultralow dose settings.

Future CT protocols & new developments

The current guidelines are mainly based on evidence and experience from clinical trials and studies in the past. Continuous efforts are made by the European

Imaging Biomarker Alliance (EIBALL) and Quantitative Imaging Biomarker Alliance (QIBA) to streamline the use and validation of imaging biomarkers like lung nodule quantification in lung cancer CT screening. The goal of these subcommittees of the ESR and RSNA is international standardization and harmonization of data acquisition (CT protocol) and analysis (quantification of lung nodules) (30,48). In particular, the QIBA provides some standards for image quality assurance, rather than specified scan parameter values for LDCT. For instance, minimum requirements for image quality defined by the resolution, edge enhancement, HU deviation, voxel noise and spatial wrapping are defined in the 'QIBA Profile: 'Small Lung Nodule Volume Assessment and Monitoring in Low Dose CT Screening'. New (ultra) low dose CT protocols then may not only be tested against the full dose protocol for nodules' sensitivity but could also be benchmarked against these general image quality parameters.

Besides the image quality assurance with the QIBA profile, the EIBALL keeps track of new developments like computer-aided detection (CAD), radiomics and deep learning in the field of lung cancer (48). The CT protocol can also have impact on the performance of these new applications. In general, use of CAD as a second reader has been found to improve the sensitivity for lung nodule detection (49). This has also shown to be beneficial in ULDCT. In a study of Takahashi *et al.* 55 patients underwent ULDCT with a tin-filter protocol. Four thoracic radiologists, with 5 to 21 years of experience, analyzed the low dose scans without and once with the help of CAD as a second-reader for the detection of solid, sub-solid and ground glass nodules of ≥5 mm (50). The sensitivity could be increased with 19% and 20% for two readers with the help of CAD, whereas for the two others readers the sensitivity was unchanged. In a study by Nomura *et al.* the performance of CAD software in ULDCT could be improved by using IR algorithms (51). Training of the CAD software on ULDCT data sets with IR may even further improve the performance of CAD, since the current CAD software was only trained on scans from low-dose protocols.

Another developing field in which the CT protocol plays an important role is radiomics. In the setting of lung cancer screening, numerous other features besides size and shape can be extracted and analyzed from the acquired CT images, that may allow differentiation between benign and malignant nodules (52). So far, the impact of the CT protocol on radiomic features for nodule characterization has been investigated in a couple of studies. In a phantom

and patients study by Lo *et al.* the effects of dose levels, IR levels and reconstruction kernels on density and texture based features of nodules were analyzed (53). Density based feature like histogram mean was the most robust feature, while other features were impacted differently by different dose level and reconstruction. The susceptibility of features for protocol changes should be taken into account when density and texture features are used to characterize nodules or nodule change. If disregarded, one might actually measure protocol settings instead of nodule characteristics. Consequently, the authors argue that CT protocol settings should be carefully controlled and only robust features used in quantification and characterization of nodules. Kim *et al.* investigated the impact of other protocol settings like slice thickness, tube current, and reconstruction kernel using a phantom with spherical nodules (54). This study showed that all scan parameters significantly affected almost all of the twenty features that were analyzed. Contrary to the former study, the authors of this study recommend standardization and/or normalization of the features that are extracted from scans acquired with different CT protocols. In a patient study by Choe *et al.* an attempt was made to normalize scans by deep learning image conversion of chest CT scans to improve reproducibility of radiomic features between soft and hard kernels (55). They showed that the reproducibility of radiomic features could be increased from 15.2% to 57.4% if image conversion was used in data set containing scans with different reconstruction kernels. However, reproducibility of features based on the same kernel scans for two readers was significantly higher with 84.3%. The authors conclude that soft and sharp kernels cannot be used interchangeably and the same reconstruction kernel is required to warrant high reproducibility of radiomic features although deep learning image conversion increased the reproducibility considerably.

New deep learning-based algorithms may not only facilitate standardization based on kernel variation, but also allow to improve the image quality of ULDCT. Research in a phantom has found no significant differences in nodule volume were found based on volume measurements on deep learning post-processed images from ULDCT and the physical nodule volume (56). Others studies have shown that deep learning denoising techniques can increase image quality compared to FBP and iterative reconstructed ULDCT images and can preserve structural details in the CT image (57,58). The high image noise present in ULDCT can thus be reduced by these new algorithms, beyond the vendor specific iterative reconstruction

techniques, while maintaining image resolution and contrast. This will enable to apply ULDCT in a wider range of screening participants and assists in standardization of CT image quality across CT systems of different vendors.

Currently, the International Association for the Study of Lung Cancer (IASLC) is developing the Early Lung Imaging Confederation (ELIC), with the goal to serve as an global open-source cloud with LDCT images (59). The ELIC cloud will include high-quality thoracic CT images, that have passed the standardized image quality processes. These high-quality images may then be used in global quantitative lung imaging studies to improve the reliability of clinical decision support in CT lung cancer screening and beyond. The new developments described in this review are very promising to accelerate and optimize the accuracy and precision of lung nodule quantification. After further research, these aspects will have to be included in the standardized protocols and recommendations for lung cancer screening. Recommendations from European, US, and global organizations that include these developments are to be awaited.

Conclusions

In the past two decades, CT lung cancer screening protocols have evolved from prefixed settings for tube voltage and tube current towards automatic tube current modulation and tube voltage selection. Current clinical guidelines provide detailed information on reconstruction settings and encourage the use of thin slices, MPR and MIP for nodule detection and quantification. Based on the guidelines, the CT protocol should result in radiation dose of <3 mGy for standard size patient. Although cautiously, radiation dose may be further decreased in ultra-low dose CT protocols with the use of IR and tin-filter to 0.3 mGy. Performance of new ultra-low dose protocols should be evaluated thoroughly. The sensitivity in relation to nodule size, density and composition should be determined. In addition, impact on volume measurement and reproducibility, as well as performance of CAD and radiomic features should be evaluated. For the latter, re-training and re-evaluation may be required for optimal use of these techniques in ultra-low dose protocols for lung cancer CT screening. Deep learning denoising techniques are promising to increase the image quality and to apply ultra-low dose CT protocols in a wider range of screening participants, and help to optimize the accuracy and precision of lung nodule quantification and management. With the expected large-scale implementation

of lung cancer screening, further standardization of (ultra) low-dose CT techniques, including acquisition, post-processing and reporting, will be required.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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