Clinical decision support system to optimise symptom management in palliative medicine

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Comparison of National Comprehensive Cancer Network and European Position Statement protocols for nodule management in low-dose computed tomography lung cancer screening in a general Chinese population

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Background: Low-dose computed tomography (LDCT) lung cancer screening often refers individuals to unnecessary examinations. This study aims to compare the European Position Statement (EUPS) and National Comprehensive Cancer Network (NCCN) protocols in management of participants at baseline screening round.

Methods: LDCT lung cancer screening was prospectively performed in a Chinese asymptomatic population aged 40–74 years. A total of 1,000 consecutive baseline LDCT scans were read twice independently. All screen-detected lung nodules by the first reader were included. The first reader manually measured the diameter of lung nodules (NCCN protocol), and the second reader semi-automatically measured the volume and diameter (EUPS volume and diameter protocols). The protocols were used to classify the participants into three management groups: next screening round, short-term repeat LDCT scan and referral to a pulmonologist. Groups were compared using Wilcoxon test for paired samples. Number of lung cancers by protocols was provided.

Results: Of the 1,000 participants (61.4±6.7 years old), 168 lung nodules in 124 participants were visually detected and manually measured in the first reading, and re-measured semi-automatically. Applying the NCCN protocol, EUPS volume and diameter protocol, the proportion of referrals among all participants was 0.6%, 1.9%, and 1.4%, respectively. The proportion of short-term repeat scans was 4.5%, 9.7% and 4.5%, respectively. Among the 10 lung cancer patients, one would have been diagnosed earlier if the EUPS volume protocol would have been followed.

Conclusions: In a first round screening in a Chinese general population, the lower threshold for referral in the EUPS protocol as compared to the NCCN protocol, leads to more referrals to a pulmonologist, with the potential of earlier cancer diagnosis. The EUPS volume protocol recommends fewer participants to short-term repeat LDCT scan than the EUPS diameter protocol. Follow-up studies should show the impact of both protocols on (interval) cancer diagnosis.

Introduction

Screening for lung cancer by low-dose computed tomography (LDCT) has been shown to prevent premature death by detecting developing cancers at an early stage (1). The National Lung Screening Trial (NLST) and the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) demonstrated a reduction in lung cancer mortality and showed the benefit of LDCT screening for lung cancer in high-risk populations (2,3).

A main challenge in LDCT lung cancer screening is that the majority of screen-detected lung nodules are benign, which results in a large number of unnecessary short-term LDCT repeat scans and referrals to a specialist for further work up (4). The NLST study reported that 96% of the screen-detected nodules referred for work-up turned out to be benign, although any non-calcified nodules ≥4 mm were regarded as positive and suspicious for lung cancer in that study (2). The number of unnecessary scans and examinations depends on the definition of indeterminate and positive findings from the LDCT scan. There are several guidelines or recommendations for management of screen-detected lung nodules, such as the Lung CT Screening Reporting and Data System (Lung-RADS) developed by the American College of Radiology (5), and the guideline developed by the National Comprehensive Cancer Network (NCCN) (6), in which diameter thresholds are provided. In addition, based on the findings from NELSON study, the European Position Statement (EUPS) on lung cancer screening proposed volume thresholds for nodule management, in which the diameter thresholds companied (7). These guidelines were mainly developed for lung cancer screening in a high risk population, and proposed inconsistent definitions for intermediate and positive nodules which require short-term repeat LDCT scan and referral to a pulmonologist, respectively, thus it is necessary to evaluate how these guidelines differ in nodule management in a general population.

The ongoing Netherlands and China Big 3 diseases (NELCIN-B3) project was initiated with one of the objectives being evaluation of the performance of NELSON and NCCN protocols in terms of false positive rate in Chinese lung cancer screening setting (8). NELCIN-B3 study provided an opportunity for the intended comparison. The aim of the current study was to compare the rate of immediate referral and short-term repeat LDCT scan between NCCN and EUPS protocols in a Chinese screening setting.

We present the following article in accordance with the STARD reporting checklist (available at https://dx.doi.org/10.21037/jtd-21-1312).

Methods

In 2017, the NELCIN-B3 project was initiated aiming to improve early detection of lung cancer, chronic obstructive pulmonary disease and cardiovascular disease. Detailed study protocols have been published previously (8,9). This prospective study was approved by the ethics committee of the leading institute of NELCIN-B3 study, namely the Committee on Ethics of Biomedicine Research of Second Military Medical University (8). Written informed consent was obtained from each participant. The NELCIN-B3 study has been registered on ClinicalTrials.gov with the registration number NCT03988322 and NCT03992833. This study conformed to the provisions of the Declaration of Helsinki (as revised in 2013).

Study population

In total 5,524 participants were prospectively recruited for LDCT lung cancer screening in the Tianjin Medical University Cancer Institute and Hospital (TJMUCIH) from June 2017 until July 2018. The inclusion criteria of participants have been described previously (8). Briefly, participants aged 40–74 years, residing in the Hexi district of Tianjin city for at least 3 years and without self-reported history of a malignant tumor were recruited. In the here presented analysis, the first LDCT scan of
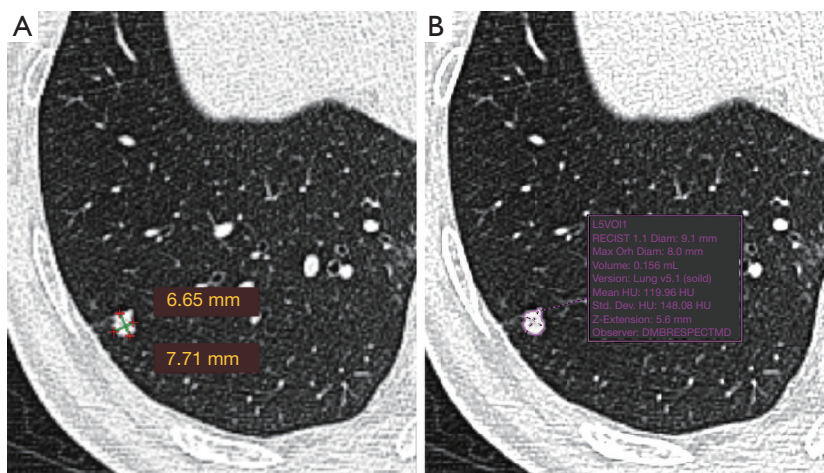
Figure 1 CT image with manual diameter measurement (A) and semi-automated volume and diameter measurement (B). CT, computed tomography.

1,000 consecutive participants at baseline were included.

CT scan protocol

The scan protocol has been described in detail previously (8). All scans were performed using the same CT system: Definition AS (Somatom Definition AS 64, Siemens Healthineers, Erlangen, Germany). Positioning of participants was head-first, supine, and with arms above the head. The CT scan was performed at end-inspiration in spiral scan mode, tube voltage of 120 kVp and a reference tube current of 35 mAs. Data were reconstructed with medium-soft (D45F) and hard (B80F) kernels at a slice thickness and increment of 1.0/0.7 mm, and with soft kernel (B30) at 2.0/1.0 mm.

Image reading and measurements

The LDCT images were read first by Chinese radiologists and the visually-detected lung nodules were measured. The detected nodules were measured for a second time by a Dutch radiologist. The first reading was performed by one of the four Chinese resident radiologists (Juxiang Ma, Debei Ma, Zhijun Li and Qingqing Diao) who were specially trained for reading LDCT images for lung cancer screening, and supervised by one of two senior Chinese radiologists (YL and XC) at TJMUCIH. Images were interpreted both at lung and mediastinal window settings. A nodule was registered and measured if the diameter (mean of maximum and perpendicular diameter)

≥4 mm. A nodule was considered part-solid when a non-solid component was visible as well as a solid part in lung window setting (window-width: 1,200 HU, window-level: –500 HU) and the solid part was also visible in mediastinal window setting (window-width: 320 HU, window-level: 35 HU). Measurement was performed in lung window setting. The maximum diameter of a nodule and its perpendicular diameter were measured manually on the axial plane in Carestream Picture Archiving and Communication Systems (PACS) v.11.0 (see the example in *Figure 1*). The second reading was performed by a radiologist (MDD) in The Netherlands with 10 years of experience in chest imaging, including experience in lung cancer screening at the University Medical Center Groningen, The Netherlands. The measurement of nodules was performed in lung window setting (window-width: 1,200 HU, window-level: –500 HU) in the second reading. The second reader used semi-automated volumetry software (MM Oncology, Syngo.via VB30, Siemens), providing the volume as well as the diameter of lung nodules (see the example in *Figure 1*). The diameter was registered in three dimensions, including maximum axial diameter, perpendicular diameter and z-axis diameter.

Nodule classification and participant management

The NCCN (6) and EUPS (7) protocols for nodule management were used to classify the screen-detected lung nodules at baseline. The NCCN protocol was applied with the manual diameter measurements. The diameter used for
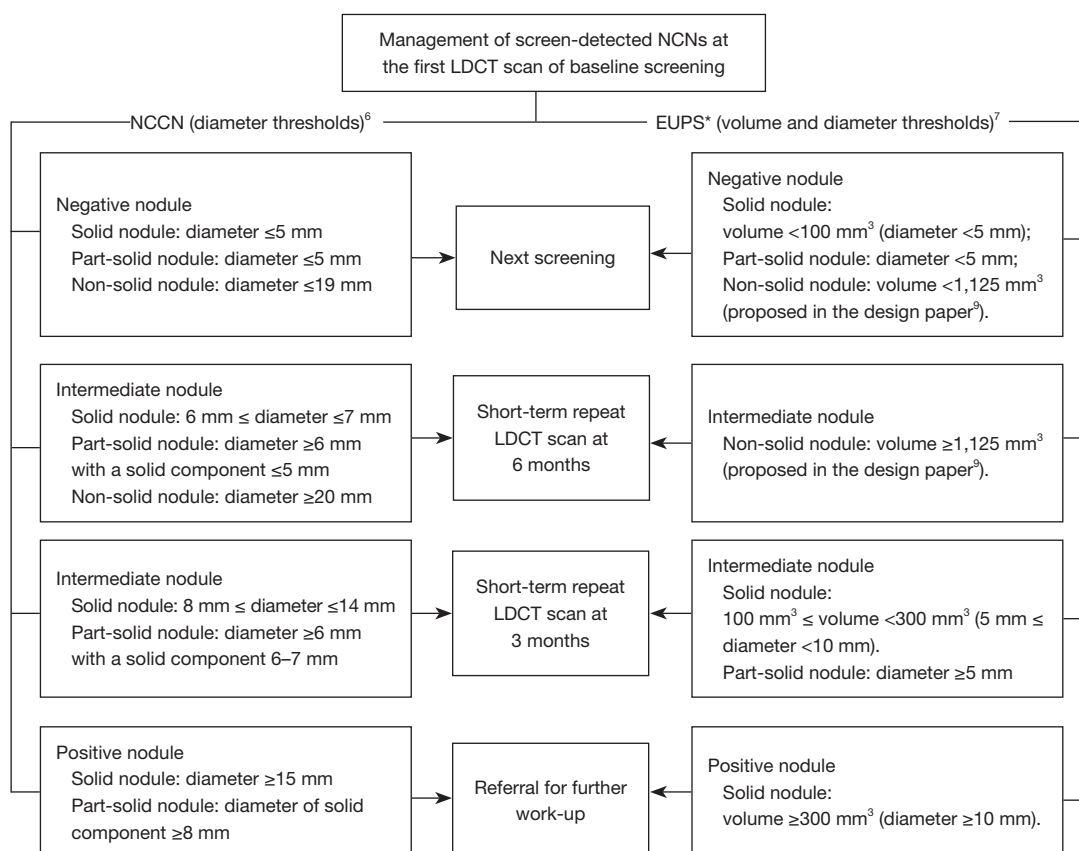
Figure 2 Management of screen-detected NCNs at initial LDCT scan in NCCN and EUPS protocols (6,7,9). *, EUPS proposed the volume thresholds for solid nodule only. In this study, the volume thresholds were also applied for part-solid nodules. NCNs, non-calcified nodules; LDCT, low-dose computed tomography; NCCN, National Comprehensive Cancer Network; EUPS, European Position Statement.

management was the mean of the maximum diameter of the nodule and its perpendicular diameter measured at the axial plane. The mean diameter was rounded to the nearest whole number according to the NCCN protocol. The EUPS protocol provided both volume and diameter thresholds. The EUPS volume protocol was applied based on the semi-automatic volume measurements and the EUPS diameter protocol was applied based on the semi-automatic diameter measurement (mean diameter of maximum axial diameter and perpendicular diameter). In the local setting, the actual management of the screenees was based on the manually measured diameter (measurements on lung window setting except the solid component of part-solid was measured on mediastinal window setting) and NCCN recommendations.

The diameter thresholds proposed by the NCCN Lung Cancer Screening (version 2. 2018) in the Clinical Practice Guidelines in Oncology are presented in *Figure 2*. The

volume and diameter thresholds of the EUPS protocol for the first scan at the baseline screening round were described in the EUPS paper (7). Briefly, for a solid nodule, a negative nodule (volume <100 mm³, diameter <5 mm) leads to next screening round at 1-year after the baseline scan, an intermediate nodule (100 mm³ ≤ volume <300 mm³, 5 mm ≤ diameter <10 mm) results in recommendation for short-term repeat LDCT scan at 3 months after the baseline scan, and a positive nodule (volume ≥300 mm³, diameter ≥10 mm) leads to referral to a pulmonologist for further work-up. EUPS paper only provided the volume thresholds for managing participants with solid nodule but not for part-solid and non-solid nodules. As described and rationalized in the design paper of NELCIN-B3 study (8), the same volume thresholds as solid nodules were applied for part-solid nodules; for a non-solid nodule with volume that exceeded 1,125 mm³, short-term repeat LDCT scan at

6 months after baseline was proposed, and for a non-solid nodule with volume <1,125 mm^3, next screening round after 1-year was proposed (*Figure 2*).

Based on the size classification of screen-detected nodules, the management of participants at baseline included next screening, short-term repeat LDCT scan (including 6- and 3-month scan after the initial scan) and referral to a pulmonologist for further work-up. For participants with multiple nodules, the nodule with the largest diameter was applied to manage the individual. Alternatives for further work-up in the actual management of screen-detected suspicious nodules included positron emission tomography (PET) or CT scans, core needle biopsy, and primary resection.

Collected features of lung nodules

Consistency (solid, part-solid or non-solid), manual maximum diameter and perpendicular diameter of lung nodules were collected from the first reading, and semi-automated volume and semi-automated diameter measurement of the nodules were collected from the second reading. For part-solid nodules, the diameter and volume of the solid component were additionally collected. The diagnosis of lung cancer among all participants with baseline nodules by the time of the second round screening (including the second round screening results) was collected through the Hospital Information System of TJMUCIH or through contact by calling. The non-cancer status was confirmed based on the second round screening results.

Sensitivity analysis

In the NCCN guideline, the average diameter of lung nodules was rounded to the nearest whole number for nodule management. To assess the effect of applying the diameter measurement with one decimal fraction (not rounding to the nearest whole number) on nodule classification and participants management, a sensitivity analysis was performed.

Statistical analysis

With an estimated effect size of 0.19 in this study, a sample size of 1,000 and an alpha error of 5%, the study will have 93% of power to detect the effect of the EUPS volume protocol on the classification to the group of short-term repeat CT or referral compared to the NCCN protocol.

The description of nodule size is presented in mean and standard deviation (SD), median and interquartile range (IQR), minimum and maximum. The classification of nodules and management of participants according to the NCCN and EUPS protocols is presented in frequency and percentage. The difference in participants classification between the two protocols was tested with Wilcoxon test for paired sample and P<0.05 was considered statistically significant. All analyses were conducted in R Statistical Software (version 3.5.1).

Results

Characteristics of participants and nodules

Among the 1,000 consecutive participants at baseline, 55.0% (n=550) were women. Mean age of the participants at baseline was 61.4±6.7 years (men: 63.1±6.1 years, women: 60.0±6.8 years). There were 219 (48.7%) current smokers, 95 (21.1%) former smokers, 136 (30.2%) never smokers in men, and 16 (2.9%) current smokers, 3 (0.5%) former smokers, 529 (96.2%) never smokers in women.

In total, 168 non-calcified lung nodules of 124 participants were registered and measured. Of the 124 participants, 63 (50.8%) were women. The mean age was 62.5±6.1 years (men: 63.8±5.6 years, women: 61.2±6.4 years). Majority (85.7%) of the screen-detected nodules were solid. For solid nodules, the median of the manual diameter measurement, semi-automated diameter measurement and semi-automated volume measurement was 5.0 (IQR: 4.4–6.0) mm, 6.2 (IQR: 5.3–7.8) mm and 92.5 (IQR: 61.0–162.2) mm^3, respectively (*Table 1*). The nodule classification by NCCN and EUPS protocols are presented in Table S1.

Lung cancer diagnosis

Among the 1,000 participants, by the time of the second round screening (including the second round screening results), 9 were diagnosed with lung cancer based on pathology results, 1 was diagnosed with suspected lung cancer by the radiologist but without confirmation from histopathology, 793 (79.3%) were not diagnosed with lung cancer and 197 (19.7%) were lost to follow-up. The 10 cancer patients included 8 diagnosed at the first screening round and 2 at the second screening round (*Figure 3*). The characteristics of the participants with lung cancer are presented in *Table 2*.

Table 1 Description of the size of the screen-detected lung nodules at the initial LDCT scan for lung cancer screening

Indicator	Manual diameter measurement* (mm)	Semi-automated diameter measurement# (mm)	Semi-automated volume measurement (mm³)
Solid nodule (n=144)			
Median (IQR)	5.0 (4.4–6.0)	6.2 (5.3–7.8)	92.5 (61.0–162.2)
Mean ± SD	5.0±4.7	7.4±5.2	600.7±3,528.1
Min	3.5	3.4	13.0
Max	41.0	44.2	39,810.0
Part-solid nodule (n=5)			
Whole nodule			
Median (IQR)	10.6 (8.5–14.9)	11.8 (11.8–17.6)	991.0 (606.0–1,082.0)
Mean ± SD	11.9±4.9	13.5±4.3	827.8±458.7
Min	6.7	8.2	146.0
Max	18.7	18.3	1,314.0
Solid component		NA	
Median (IQR)	7.0 (6.0–11.0)		583.0 (346.0–702.0)
Mean ± SD	8.2±3.7		506.8±269.4
Min	4.0		124.0
Max	13.0		702.0
Non-solid nodule (n=19)			
Median (IQR)	6.5 (5.5–7.5)	7.9 (6.2–9.9)	110.0 (91.5–211.0)
Mean ± SD	7.3±3.2	8.9±4.0	352.8±746.0
Min	4.1	4.7	55.0
Max	17.0	21.7	3,323.0

*, the diameter was the mean of the maximum diameter of the nodule and its perpendicular diameter measured at axial plane; #, the diameter was the mean of the maximum axial diameter and orthogonal diameter of the nodule. LDCT, low-dose computed tomography; IQR, interquartile range; SD, standard deviation; NA, not available.

Comparison of NCCN and EUPS protocols at participant level

The proportion of referrals to a pulmonologist in the participants according to NCCN protocol was lower than that according to EUPS volume protocol (0.6% *vs.* 1.9%). The proportion of short-term repeat scans was similar according to the two protocols (4.5% *vs.* 4.5%) (*Table 3*).

The proportion of referrals to a pulmonologist in the participants according to EUPS volume protocol and EUPS diameter protocol was similar (1.4% *vs.* 1.9%). But the proportion of short-term repeat scans according to EUPS volume protocol was lower than the EUPS diameter protocol (4.5% *vs.* 9.7%). The conclusion remained when

restricted to participants with solid nodule (*Table 3*).

Among the 949 participants referred to the next screening round in the NCCN protocol, 6.3% (60 participants) and 1.7% (16 participants) would require a short-term repeat CT scan if applying the EUPS diameter and volume protocol, respectively. Among the 45 participants needing short-term repeat CT according to the NCCN protocol, 22.2% (10 participants) and 28.9% (13 participants) would be referred to a pulmonologist if applying the EUPS diameter and volume protocol, respectively. The management differed significantly between the NCCN and EUPS protocols (P<0.001) (*Table 4*).

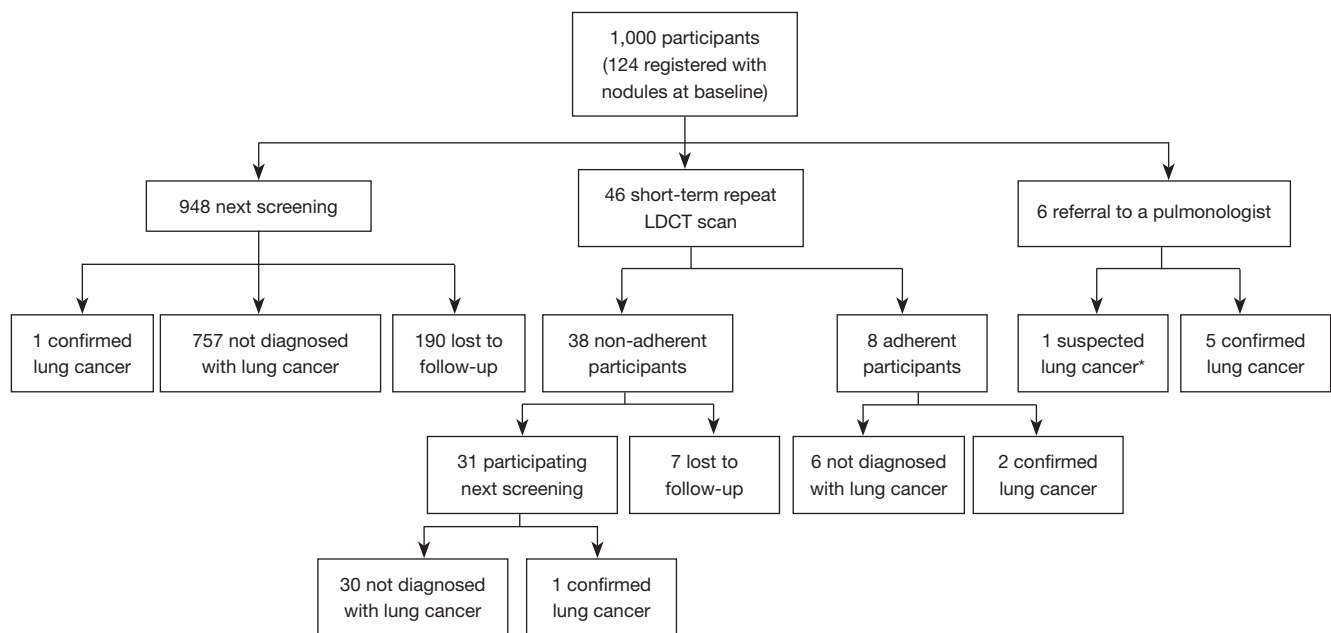Regardless of which protocol was applied, 10 participants

Figure 3 The actual management for all participants and lung cancer diagnosis until (including) the second round screening. *, suspected lung cancer according to the radiologist but without confirmation from histopathology. LDCT, low-dose computed tomography.

with lung cancer were detected through screening. One patient (No. 8) with a solid malignant nodule required short-term follow-up by NCCN protocol but required referral for further work-up by EUPS volume protocol, which means that EUPS volume protocol would detect this malignant lesion earlier (*Table 2*).

Sensitivity analysis

Compared to applying the average diameter rounded to the nearest whole number, applying the average diameter with one decimal fraction to the NCCN protocol led to fewer solid nodules (32, 22.2% *vs.* 49, 36.0%) being classified as intermediate nodules (Table S2). Consequently, fewer participants would require short-term repeat CT scan (32, 3.2% *vs.* 45, 4.5%; Table S3).

Discussion

In this study, we compared the management of participants when applying NCCN and EUPS protocols in a general Chinese population. We found that, in LDCT lung cancer screening setting, the number of referrals based on the EUPS volume protocol was 3 times higher than that based on the NCCN protocol; the number of short-term repeat

scan based on the EUPS diameter protocol was double compared to that based on the EUPS volume protocol. One out of the 10 lung cancer patients would have been diagnosed earlier if followed the EUPS volume protocol.

There are some explanations for the larger number of referrals according to the EUPS volume protocol as compared to the NCCN protocol (1.9% *vs.* 0.6%). The main explanation was that the EUPS protocol recommends a less stringent threshold in the definition of a positive nodule (volume ≥300 mm^3) than the NCCN protocol (diameter ≥15 mm). If assuming that nodules are spherical, the positive volume threshold is equivalent to 8.3 mm in diameter, which is much lower than the definition of the NCCN protocol. Therefore, more nodules required referral to a pulmonologist in the EUPS protocols in this study. In addition, the approach for measuring nodule diameter might contribute to the difference in number of referrals. The manual diameter measurements were smaller than the semi-automated diameter measurement in this study, suggesting underestimation of referral rate based on manual measurements.

Using semi-automated measurements of volume and diameter, at nodule level, the EUPS volume protocol was associated with a lower number of combined intermediate and positive nodules than the EUPS diameter protocol (at

Table 2 Characteristics of participants diagnosed with lung cancer until (including) the second screening round

Patient	Sex	Age (years)	Nodule type at first scan	Nodule size at first scan			Round at diagnosis	Stage	Histology
				Manual diameter (mm)	Semi-automated diameter (mm)	Volume (mm³)			
1	Men	65	Solid	41	44.2	39,810	First round (direct referral)	IIA	ADC
2	Men	62	Solid	18	19.2	1,697	First round (direct referral)	IA	ADC
3	Men	72	Part-solid	19 (solid component: 11 mm&)	17.6	1,314	First round (direct referral)	IA	ADC
4	Men	63	Non-solid	17	21.7	3,323	First round (direct referral)*	IA	ADC
5	Women	63	Solid	29	29.6	6,648	First round (direct referral)	IB	ADC
6	Women	61	Solid	8	8.3	233	First round (short-term repeat LDCT scan at 3-month)	IA	ADC
7	Women	57	Part-solid	15 (solid component: 13 mm#)	18.3	991	First round (short-term repeat LDCT scan at 3-month)	IA	ADC
8	Women	61	Solid	11	12.2	681	Second round (short-term repeat LDCT scan at 6-month)	IA	ADC
9	Men	63	Solid	18	14.6	702	Second round (direct referral)	IA	ADC
10**	Men	63	Solid	33	39.6	13,494	First round (direct referral)	Suspected IV	Unknown

&, solid component on mediastinal window was 8 mm; *, although manual diameter <19 mm, referral was recommended based on other features of the nodule; #, solid component on mediastinal window was 6 mm; **, suspected lung cancer according to the radiologist but without confirmation from histopathology. ADC, adenocarcinoma; LDCT, low-dose computed tomography.

participant level: 6.4% *vs.* 11.1%, at nodule level: 42.9% *vs.* 84.5%). This finding is consistent with another study, in which 34% of nodules were classified to Lung-RADS 3 or more when using semi-automated volume, and 52% were classified to these groups when using semi-automated diameter (10). Similar results were reported by NELSON study. At participant level, the proportion of short-term repeat LDCT scans and referrals using the EUPS volume thresholds was lower than using the equivalent EUPS diameter thresholds (8% *vs.* 22% for short-term repeat, 5% *vs.* 5% for referral) (11).

Applying the EUPS volume protocol, we found 4.5% participants in need of a short-term repeat scan and 1.9% in need of referral to a pulmonologist, respectively. The figures in the first screening round of NELSON study showed 8% short-term repeat scans and 5% referrals (11). The lower proportion of short-term repeat scan and referral in our study is probably due to the fact that we included a lower risk population (general population aged between

40 and 74 years, including a substantial proportion of never-smokers) compared to NELSON study in which heavy smokers were included.

Applying the NCCN protocol, 0.6% participants needed referral. This finding is similar to a study performed in Shanghai (12) but lower than a study in Sichuan, China (13). According to the report of lung cancer screening in a general population in Shanghai, 0.6% of included participants required referral to a pulmonologist (diameter ≥15 mm) (12). The lung cancer screening study in Sichuan reported 1.6% of participants with nodule >15 mm (13). The higher proportion in the study in Sichuan is probably due to that the high risk population was included. Furthermore, as shown in the sensitivity analysis, when the average diameter was not rounded to the nearest whole number, the number of solid nodules being classified as intermediate decreased by 35% from 49 to 32, which suggested a potential decrease in the number of unnecessary follow-up LDCT scans.

Table 3 Management of participants and lung cancer diagnosis after the first LDCT scan at baseline screening round according to NCCN and EUPS protocols

Management	NCCN protocol	EUPS diameter protocol	EUPS volume protocol
All participants (n=1,000)			
Next screening	949 (94.9%)	889 (88.9%)	936 (93.6%)
Short-term repeat (3/6 months)	45 (4.5%)	97 (9.7%)	45 (4.5%)
Referral to a pulmonologist	6 (0.6%)	14 (1.4%)	19 (1.9%)
Participants with solid nodule (n=103)			
Next screening	57 (55.3%)	13 (12.6%)	45 (43.7%)
Short-term repeat (3/6 months)	42 (40.8%)	76 (73.8%)	43 (41.7%)
Referral to a pulmonologist	4 (3.8%)	14 (13.6%)	15 (14.6%)
Participants with part-solid nodule (n=5)			
Next screening	0	0	0
Short-term repeat (3/6 months)	3	5	1
Referral to a pulmonologist	2	0	4
Participants with non-solid nodule (n=16)			
Next screening	16	0	15
Short-term repeat (3/6 months)	0	16	1
Referral to a pulmonologist	0	0	0
Participants without nodules (n=876)			
Next screening	876	876	876
No. of lung cancer diagnosis until (including) second round	10	10	10

LDCT, low-dose computed tomography; NCCN, National Comprehensive Cancer Network; EUPS, European Position Statement.

Table 4 Disagreement of NCCN and EUPS protocols for management of participants after the first LDCT scan at baseline screening (n=1,000)

NCCN protocol	EUPS diameter protocol			EUPS volume protocol		
	Next screening	Short-term repeat (3/6 months)	Referral to a pulmonologist	Next screening	Short-term repeat (3/6 months)	Referral to a pulmonologist
Next screening	889	60	0	933	16	0
Short-term repeat (3/6 months)	0	35	10	3	29	13
Referral to a pulmonologist	0	2	4	0	0	6

Wilcoxon test for paired sample: P<0.001 for NCCN *vs.* EUPS diameter, P<0.001 for NCCN *vs.* EUPS volume. NCCN, National Comprehensive Cancer Network; EUPS, European Position Statement; LDCT, low-dose computed tomography.

The strength of this study was the well-defined general population for lung cancer screening and the prospective study design. Furthermore, manually-measured diameters were collected in addition to semi-automated diameter and volume measurements and all of them were applied in the management protocols for comparison. There were also some limitations in this study. First, the lower threshold in the EUPS volume protocol results in more referrals for

further work-up, while also allows the possibilities of earlier cancer diagnosis (such as the patient No. 8). But because of the small number of participants with lung cancer, the sensitivity and specificity of the protocols were not calculated and a reliable conclusion regarding the performance of the evaluated protocols could not be drawn with the present study. In addition, about 20% of participants were lost to follow-up, their cancer status cannot be determined. Second, the EUPS protocol was developed for the early diagnosis of lung cancer in a high risk population. The included general population may not be eligible for such a protocol due to the low risk of lung cancer. Third, EUPS volume protocol was developed for solid nodule only. In this study, the volume thresholds for solid nodule were also applied for part-solid nodule. But even restricting the analysis in participants with solid nodule, the conclusion remained. Fourth, the main strength of EUPS volume-based protocol was the high sensitivity in detecting the increase of tumor growth, while we could not evaluate that in this Chinese population due to lack of the volume measurements from a second scan. It will be evaluated in our future studies. Fifth, the manual and semi-automatic measuring for nodule size were performed by different radiologists. The inter-reader variability was not evaluated in this study, but could affect the manual diameter and volume assessment of a lung nodule, especially, the inter-reader variability for semi-automated volume measurements is 11% lower than that for manual diameter measurements (14).

In conclusion, in a Chinese general population, the EUPS volume protocol leads to a higher pulmonologist referral rate than the NCCN protocol in LDCT lung cancer screening setting due to the less stringent criteria for referral. The less stringent criteria in the EUPS volume protocol are also associated with a probability of earlier cancer diagnosis. EUPS volume protocol is associated with a lower rate of short-term repeat LDCT scan and referral compared with the EUPS diameter protocol. In our future study, more data in lung cancer diagnosis will be available to allow assessing the performance of the evaluated protocols in a general population. Potentially, both diameter and volume protocols should be adjusted for low risk population, given that the referral rate may be too high in comparison to number of lung cancers found in a general population compared to a high risk population.

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://dx.doi.org/10.21037/jtd-21-1312

Data Sharing Statement: Available at https://dx.doi.org/10.21037/jtd-21-1312

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/jtd-21-1312). The authors have no conflicts of interest to declare.

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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Committee board on Ethics of Biomedicine Research of Second Military Medical University (No. 2018SL028) and informed consent was taken from all the participants.

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Table S1 Classification of screen-detected lung nodules at the first LDCT scan of baseline screening using NCCN and EUPS protocols

Nodule classification	NCCN protocol		EUPS diameter protocol		EUPS volume protocol	
	Diameter threshold (mm)	Manual diameter*, number (%)	Threshold (mm)	Semi-automated diameter$, number (%)	Threshold (mm³)	Semi-automated volume, number (%)
Solid nodule						
Negative nodule	≤5	91 (63.2)	<5	25 (17.4)	<100	78 (54.2)
Intermediate nodule	≥6 & ≤14	49 (34.0)	≥5 & <10	104 (72.2)	≥100 & <300	48 (33.3)
Positive nodule	≥15	4 (2.8)	≥10	15 (10.4)	≥300	18 (12.5)
Part-solid nodule						
Negative nodule	≤5	0 (0.0)	<5	0 (0.0)	<100	0 (0.0)
Intermediate nodule	≥6 with solid part ≤7	3 (60.0)	≥5	5 (100.0)	≥100 & <300	1 (20.0)
Positive nodule	Solid part ≥8	2 (40.0)	–	–	≥300	4 (80.0)
Non-solid nodule						
Negative nodule	≤19	19 (100.0)	<5	1 (5.3)	<1,125	18 (94.7)
Intermediate nodule	≥20	0 (0.0)	≥5	18 (94.7)	≥1,125	1 (5.3)
Overall						
Negative nodule	–	110 (65.5)	–	26 (15.5)	–	96 (57.1)
Intermediate nodule	–	52 (30.9)	–	127 (75.6)	–	50 (29.8)
Positive nodule	–	6 (3.6)	–	15 (8.9)	–	22 (13.1)

*, average diameter rounded to the nearest whole number; $, average diameter. LDCT, low-dose computed tomography; NCCN, National Comprehensive Cancer Network; EUPS, European Position Statement.

Table S2 Classification of screen-detected lung nodules at the first LDCT scan of baseline screening using NCCN protocol (without rounding the average diameter to the nearest whole number)

Nodule classification	Diameter threshold (mm)	Manual diameter*, number (%)
Solid nodule		
Negative nodule	<6	108 (75.0)
Intermediate nodule	≥6 & <15	32 (22.2)
Positive nodule	≥15	4 (2.8)
Part-solid nodule		
Negative nodule	<6	0 (0.0)
Intermediate nodule	≥6 with solid part <8	3 (60.0)
Positive nodule	Solid part ≥8	2 (40.0)
Non-solid nodule		
Negative nodule	<20	19 (100.0)
Intermediate nodule	≥20	0 (0.0)
Overall		
Negative nodule	–	127 (75.6)
Intermediate nodule	–	35 (20.8)
Positive nodule	–	6 (3.6)

*, average diameter not rounded to the nearest whole number. LDCT, low-dose computed tomography; NCCN, National Comprehensive Cancer Network.

Table S3 Management of participants and lung cancer diagnosis after the first LDCT scan at baseline screening round according to NCCN protocol (without rounding the average diameter to the nearest whole number)

Management	NCCN protocol
All participants (n=1,000)	
Next screening	962 (96.2%)
Short-term repeat (3/6 months)	32 (3.2%)
Referral to a pulmonologist	6 (0.6%)
Participants with solid nodule (n=103)	
Next screening	70 (68.0%)
Short-term repeat (3/6 months)	29 (28.2%)
Referral to a pulmonologist	4 (3.8%)
Participants with part-solid nodule (n=5)	
Next screening	0
Short-term repeat (3/6 months)	3
Referral to a pulmonologist	2
Participants with non-solid nodule (n=16)	
Next screening	16
Short-term repeat (3/6 months)	0
Referral to a pulmonologist	0
Participants without nodules (n=876)	
Next screening	876
No. of lung cancer diagnosis until (including) second round	10

LDCT, low-dose computed tomography; NCCN, National Comprehensive Cancer Network.