Review Article

Diameter versus volumetry: a narrative review on current recommendations to measure and monitor screening detected lung nodules

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Abstract: Lung cancer (LC) is a leading cause of oncological death worldwide. Up to 70% of patients suffers from advanced disease at the time of diagnosis, which limits curative options. Early diagnosis of LC by means of low dose computed tomography (LDCT) has been proven effective by different LC screening (LCS) trials, which show a 20–30% mortality reduction in high-risk subjects. LDCT allows identification and longitudinal evaluation of pulmonary nodules (PNs), with subsequent stratification of LC risk based on their size and growth rate. Adequate management of screen-detected PN mostly relies on nodule density and sizing. Accurate size measurement is mandatory to determine the risk for malignancy, the recall rate and thus, the feasibility and the efficacy of LCS. Size and growth rate of PN can be determined by measuring either their diameter or volume. This narrative review article aims at reporting strengths and weaknesses of the two PN sizing approaches in LCS, and to discuss possible implications of PN size over- and underestimation.

Keywords: Lung cancer screening (LCS); low dose computed tomography (LDCT); pulmonary nodule (PN); diameter; volumetry

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Introduction

Background

Lung cancer (LC) is a leading cause of death, accounting for up to 18,4% of all cancer-related deaths worldwide (1). The high mortality rate of LC is due to delay in diagnosis, with roughly 75% of cases diagnosed at advanced stages (IIIC or metastatic stage IV), limiting curative options and thus, affecting the prognosis (1,2). If, indeed, the majority of patients with stage IV LC die within 5 years from the diagnosis, those with stage IA have a >75% chance of survival over 5 years (3). Tobacco smoking represents the major risk factor for LC (4) and thus a major criterion for selection of lung cancer screening (LCS) participants. Smoking history is used in several risk models along with further integration by older age, family history of LC, and gender (5). Reduction of LC mortality by smoking cessation (also known as primary prevention) represents

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the optimal approach to control LC occurrence and further smoking related systemic diseases (6,7). Unfortunately, the literature shows that smoking cessation is particularly hard to pursue (8). This is one among other reasons behind the concept of coupling primary and secondary prevention for early diagnosis (9). Early diagnosis of LC by means of low dose computed tomography (LDCT) has been proven to be effective by different LCS trials, showing a 20–30% mortality reduction in high-risk subjects (1,10,11). The purpose of LCS is the detection of pulmonary nodules (PNs) harboring malignant biological behavior, representing early-stage LC candidate for curative surgery (10,12).

In the last two decades, LCS trials enrolled more than 100,000 subjects, with PNs being detected in up to 66% of them (13-15). The vast majority of screen-detected PN, however, does not represent clinically relevant lung cancers (16-18). A systematic approach to PN is key to limit both overdiagnosis and delayed cancer diagnosis. Safe management of screen-detected PN is ensured by appropriate screening intervals and adequate work-up (e.g., biopsy, positron emission tomography (PET)-CT scan). PN management mostly relies on density and size, whose accurate measurement is pivotal for several reasons: (I) to determine the risk of malignancy at baseline CT; (II) to correctly assign LDCT outcome and appropriate follow-up algorithm; and (III) to detect change in size on subsequent LDCT (19). Size and growth rate of PN can be determined by measuring either their diameter or volume. Due to its simplicity and applicability, diameter measurement has been widely used in the early phases of LCS by CT. Following the advent of thin slice CT and the availability of three dimensional segmentation software, the semi-automated volumetric approach has become a valid alternative and it is currently deemed as more accurate and reproducible (20).

Objectives

This narrative review article aims at reporting strengths and weaknesses of the two PN sizing approaches in LCS, and to discuss possible implications of PN size over- and underestimation. Future perspectives on LCS implementation within national health systems will also be discussed.

Methods

We referred to PubMed and the Cochrane database website to retrieve English-written relevant articles. Systematic reviews, meta-analyses, original articles and randomized clinical trials published up to November 2020 were considered.

We present the following article in accordance with the Narrative Review reporting checklist (available at: https://dx.doi.org/10.21037/shc-21-5).

Diameter *vs.* volume in LCS trials

Although LCS trials are fairly similar in their eligibility criteria, such as age and smoking history, they differ substantially in the (I) total number of screens performed, (II) screening intervals, and (III) radiologic criteria used for PN detection and classification (*Table 1*) (21-24,26-31).

Management of PN relies on two main features: density and size. The density of PN differentiates between solid and sub-solid, these two categories reflect different risk profile. Size represents the most important parameter for predicting LC risk and correctly assigning LDCT outcome categories, notably in solid nodules (19). The risk of malignancy increases with nodules of greater size, being less than 1% for nodules measuring 5 to 6 mm and reaching up to 11.1% for those of 10–15 mm in diameter (32). Nodule size can be assessed by measuring either its diameter or volume (10,33). For diameter measurements, PN are considered as two-dimensional structures, whereas volumetry encompasses their three-dimensional geometry (34). According to the diameter approach, growth is called based on a fixed threshold of 2 mm, while for the volume reference a relative increase of 25% is established for definition of actual nodule growth (35-37).

Diameter measurements are commonly used in LCS and clinical practice (38). In the NLST and several other LCS trials, maximum axial diameter was used for size determination of screen-detected PN (*Table 1*). Volumetry, however, is currently the recommended metric for nodule sizing, and volumetric thresholds have recently been encompassed by the Lung Imaging Reporting and Data System (LungRADS, version 1.1), whereas the previous version (issued in year 2014) only recommended the use of nodule mean diameter (19,39).

Diameter-based approach

The major advantage of measuring nodule diameter is that it can be determined for all PN, regardless of their shape (regular or irregular), density (solid, part-solid or non-solid), and contact with solid structures (40). Manual measurement

Table 1 Summary of the protocol, inclusion criteria and nodule measurement approach of the major lung cancer screening trials

Screening trial	Number of participants	Age of subjects (years)	Smoking history	Screening method	Nodule assessment (diameter/volume)
NLST	53,456	55–74	>30 pack-years of cigarette smoking history; former smokers: quit smoking within the previous 15 years	Baseline and two annual screen by either LDCT (26,722 participants) or CXR (26,732 participants)	Diameter
NELSON (21)	15,422	50–75	≥15 cigarettes per day for ≥25 years or ≥10 cigarettes per day for ≥30 years (42 pack-years)	Baseline, 1-, 2-, and 4-year rounds by CT	Volume (or diameter for pleural based nodules)
DLCST (22)	4,104	50–70	≥20 pack-years	Baseline and annual screen by LDCT for 4 years	Diameter
MILD (23)	4,099	>49	≥20 pack-years	Annual or biennial screen by LDCT for a median period of 6 years	Volume
UKLS (24)	4,055	50–75	As for formal individual risk stratification by LLP (25)	Single screen by LDCT	Volume (or diameter in case of unavailability of segmentation software)
LUSI (26)	4,052	50–69	≥15 cigarettes per day for ≥25 years or ≥ 10 cigarettes per day ≥30 years	Baseline and annual screen by LDCT for 4 years	Diameter
ITALUNG (27)	3,206	55–69	≥20 pack-years	Annual screen by LDCT for 4 years	Diameter
DANTE (28)	2,450	60–74	≥20 pack-years	Baseline CXR and 5 annual screen by either LDCT or clinical review	Diameter
Depiscan (29)	765	50–75	≥15 cigarettes/day for ≥20 years	Baseline and two annual screen by either LDCT or CXR	Diameter

LDCT, low dose computed tomography.

of nodule diameter is commonly performed with electronic calipers, determining either the largest diameter or the average of the longest diameter and its perpendicular longest axis. This latter method is to be preferred, since PN are not necessarily spherical in shape (33). Moreover, if inter- and intra-observer variability is expected to range between 1.5–2 mm with this coupled measurement, it increases to almost 3 mm by using a single diameter (41,42).

Regardless of the approach used, however, bidimensional measurement is affected by poor inter- and intra-observer agreement, particularly for nodules displaying irregular shape for which a proper boundaries delimitation might be difficult (43). Han *et al.* showed that the inter-reader variation in mean diameter of smooth and lobulated nodules was ±1.9 and ±2.0 mm, whereas for spiculated and irregular nodules ±3.4 and ±4.5 mm (44). Numerous studies have demonstrated that such approach limits nodule sizing accuracy both at baseline (leading to different management approaches) and at subsequent screening rounds (41,45,46), where small variations in size may have significant implications (e.g., an increase of 2 mm for a nodule of 4 mm at baseline represents a 50% increase). Interobserver variability can be partly controlled by measuring the diameters in the axial plane (47), but the selection of the axial slice where the nodule shows the maximum diameters represents a source of variability (45).

Volume-based approach

European LCS trials demonstrated that nodule volumetry is an accurate predictor of LC risk, associated with lower inter- and intra-observer variability as compared with

manual bidimensional measurement (48,49). Volume can be determined through a diameter-based estimation or by using automated software. Although automated volumetry carries the risk of errors, these are about 10 times smaller than those of manual measurement (45,50,51). Heuvelmans *et al.* compared the two techniques and observed that the diameter-based approach leads to a substantial overestimation of PN volume, ranging from 47% to 85% (42). Such a discrepancy is probably due to PN not being perfectly spherical in shape (34). Analogously, de Margerie-Mellon *et al.* reported that the diameter-based assessment of nodule volume may overestimate the actual growth of pulmonary adenocarcinoma presenting as subsolid nodules (SSN) (52). Gierada *et al.* have recently observed how the use of semiautomated CT volumetry improved interobserver agreement and enabled classification of more PN into lower LungRADS categories than the use of either manual or semiautomated diameter measurements (48).

Although volumetry is more accurate and reproducible, volumetric software may not be available to all radiologists and its use can be rather time-consuming. Mets *et al.* demonstrated that only a minority of radiologists (8%) uses volumetric software in their clinical practice (47). Different volumetry software packages (VSPs) vary in nodule size estimation. Provided that different LCS programs would not necessarily have access to the same software, Soo *et al.* demonstrated that nodule size thresholds for LCS recalls depend on the software used, emphasizing the need for radiologists to ensure that the VSP used in their LCS programme is comparable to those used to set guidelines (49). This variability makes the use of the same software a necessity (33).

Volumetric assessment is highly influenced by the quality of LDCT dataset. The use of thin sections and medium-smooth or medium-sharp kernel is recommended to increase spatial resolution while reducing noise, artifacts, and partial volume effect (53,54). Variability in nodule volumetry using LDCT is comparable to that of standard dose technique. Paks *et al.* demonstrated that all solid PN (>2 mm) depicted on LDCT were detected by means of ultra-low dose CT (ULDCT) as well, and that differences in bidimensional and volume measurements were minimal between the two techniques (55).

The variability of volumetric measurement is expected to range around 25%, but it increases in case of small nodules, nodules in contact with solid structures and concurrent pulmonary emphysema (33). The reproducibility of volume measurement can be affected by features unrelated to nodule size and location, such as inadequate respiratory maneuvers (e.g., expiratory acquisition increases nodule volume). Hence, providing screenees with clear instructions on how the scan apnea should be performed is essential (56).

Focus on subsolid nodules

SSN deserve special attention because of their irregular shape and density heterogeneity, which represent a challenge both for detection and measurement. SSN is defined as a nodule that does not entirely obscure the underlying vessels and bronchi; this is classified into two different subcategories: non-solid nodules (NSN, also known as ground-glass nodules) and part-solid nodules (PSNs), the latter containing both non-solid and solid components (57). Recent studies demonstrated a moderate inter- and intra-observer agreement in the classification of SSN, with discrepancy mostly caused by visual evaluation (presence and size) of the solid component (58). Most persistent PSNs harbor malignant behavior. The Early Lung Cancer Action Project (ELCAP) reported a 63% malignancy rate among PSN, significantly higher than that of solid nodules (7%) (59). The non-solid part usually represents either *in situ* or minimally invasive adenocarcinoma, whereas the solid component reflects the invasive component (60,61). The use of lung widow setting, and sharp filter is recommended to accurately measure the solid component, because mediastinal window setting may lead to underestimate such component (53,62).

CT attenuation has been proposed as a valid parameter to assess growth of SSN being the increase of solid component correlated with a rising risk for malignancy (63). Density measurement may be performed both by manual measurement and by computation of mean density and translation into mass estimate for longitudinal trajectory. Evidences, however, are still limited and larger series will be necessary to generalize preliminary results.

In PSNs, size of both the whole nodule and its solid component is an important indicator of their risk of malignancy. Detection and segmentation, however, are not easily performed on CT, especially for juxta-vascular SSN (45). The presence of vessels encompassed by the nodule can affect nodule sizing, being vessel attenuation similar to that of the solid component. To overcome this limitation, Charbonnier *et al.* proposed a method based on voxel classification to automatically differentiate the solid component of SSN from vessels (64). Volumetry represents an optimal tool for SSN sizing, despite some extra variability compared with solid nodules. Kamiya *et al.* showed that the

volumetry of the solid component in subsolid lung cancer correlates with the risk of recurrence after surgery more than the diameter of the solid component (65).

The sensitivity of computer-aided detection (CAD) software used to be quite poor, but it currently ranges between 54% and 70%, making their use safe and advisable in SSN as well as in solid nodules (66). Silva *et al.* compared manual and semiautomatic detection of SSN diameters in the MILD trial and demonstrated complementary performance of the two methods. Although the sensitivity of the semiautomatic approach was higher, visual confirmation was necessary to reduce the risk of false positive results (67), suggesting that the two approaches ought to be used complementarily in SSN, especially in PSN.

The importance of accurate nodule sizing

Accuracy in nodule sizing is mandatory: size overestimation might lead to unnecessary work-up, with subsequent additional LDCT recalls as well as non-invasive (e.g., PET-CT) and invasive (e.g., biopsy) work-up, whereas underestimation could result in false negative LDCT outcomes and delayed diagnosis. Of note, nodule size might also influence FDG-PET results. It has been demonstrated that uptake values are prone to underestimation for PN smaller than 8 mm (likely due to partial volume effects), leading to false-negative results (68). Beside size, density may affect PET-CT interpretation, causing SSN to be falsely interpreted as negative (32). Moreover, new solid nodules detected at subsequent screening rounds (incidental nodules) have a higher risk for malignancy than those detected at baseline (prevalent nodules) and should be managed more aggressively, for example by using lower volume cutoff values, which was proposed at 30 mm^3 based on the NELSON trial (69).

Several factors are thought to hamper the implementation of LCS within national health systems. Among them, sustainability and cost-efficacy are the most important. Indeed, diagnostic work-up and short-term recalls result inevitably in increasing economic and psychological burden, as well as risk from biopsy or resection of a benign lesion (70-72). Notably, it has been reported a 3.4% death rate within two months after an invasive diagnostic procedure (e.g., bronchoscopy or needle biopsy) (73). Hence, limiting overdiagnosis, intended as overdetection of indolent pathology, is essential in LCS to avoid overtreatment. In NLST, the rate of overdiagnosis was 20% for screen-detected cancers and 80% for screen-detected lepidic adenocarcinoma (74), showing that the risk of overdiagnosis is higher for slow growing cancers. Several strategies have been proposed to reduce the risk of overdiagnosis and overtreatment. These include the use of multidimensional stratification risk models, volume doubling time (VDT), long term active surveillance of SSN and longer screening intervals (12,75). Silva *et al.* have recently reported that the risk of LC in LungRADS v1.1 category 1 or 2 was substantially lower than in category 3, notably as low as 0.3% at 2 years, showing the potential for a longer than 1 year screening interval in up to 80% of NLST-eligible subjects (76).

VDT

Growth of a PN refers to an increase in size between two given CT examinations. Nodule growth rate is considered an independent risk factor for LC in screen-detected PN, allegedly the strongest predictor of risk (77). The optimal prediction of the likelihood of LC is granted by longitudinal assessment of VDT (33). Software-calculated VDT has a higher specificity (90%) and sensitivity (91%) in malignancy evaluation rather than manual caliper measurements (sensitivity 54%) (78). VDT is expressed in days and can be calculated by using a simple exponential growth model that assumes uniform three-dimensional tumor growth, from the difference in nodule diameter (or volume) between baseline and follow-up CT, and the time interval between the two examinations (41). VDT is not meant to be calculated before three months from the previous assessment, because this can lead to either over- or underestimation of the risk for LC. As mentioned above, measurement accuracy is crucial in LCS. Even small variations in nodule sizing might result in significantly inaccurate VDT (33,45).

Malignant PN tend to grow rapidly (VDT <400 days) but there are not strict rules. Benign PN might indeed show a rapid growth (VDT <400 days) as well as malignant ones might grow slowly (VDT >400 days) or even remain stable for a considerable period of time (77).

Reporting and management recommendations

The process of nodule work-up is based on clear communication between radiologists and other medical specialists. The use of standardized terminology prevents ambiguity and facilitates comparability of reports. Structured reporting, which ensures that all relevant findings are addressed, is highly ranked for the purpose of

clear communication between radiologists and clinicians, in many fields of thoracic and extra-thoracic radiology (79,80). Over the last two decades, several scientific societies have released PN management guidelines in order to standardize LDCT interpretation and reporting, and thus, to appropriately guide screen-detected nodule work-up (12). Among them, the most widely used are those proposed by the American College of Radiology (ACR) and the British Thoracic Society (BTS).

According to the LungRADS proposed by the ACR, PN are classified into different risk categories based on their size. In 2019, an updated version of LungRADS, named LungRADS v1.1, was released. The new version presents some important novelties, which reflect new evidences and advances in imaging technology. The major novelty is represented by the introduction of volume cutoff values for LungRADS categories assignment, added to diameter measurements (40). The new version also provides strict indications on how nodule measurement should be performed and recorded (e.g., long and short axis must be measured to one decimal point and the mean nodule diameter reported to one decimal point, whereas it was recommended to report the average diameter—of long and short axis diameters—rounded to the nearest whole number). Other modifications are related to (I) size threshold for pure NSN, raised from 20 to 30 mm, (II) removal of C-modifiers category (since patients diagnosed and treated for LC have annual chest CT for disease surveillance and not for screening), (III) definition of perifissural nodules, (IV) management of category 4B new large nodules developed on an annual repeat screening CT, for which one-month LDCT may be recommended to address potentially infectious or inflammatory diseases.

In 2015, the BTS released guidelines for PN investigation and management, proposing two main algorithms, based on nodule density (solid and subsolid). These two algorithms encompass both diameter and volume cutoffs for LDCT category assignment, analogously to the new version of LungRADS, but it is stated that volumetry is to be preferred as measurement method. BTS guidelines also include the use of two malignancy prediction calculators, namely Brock (also known as PanCan model) and Herder model, to better characterize the risk of malignancy (5,35).

A summary of the algorithms used by the main LCS trials for management of PN is reported in *Table 2* (21,26,27,31,36,81-83).

Future perspectives

The implementation of LCS within national health systems will inevitably lead to an increased workload. Radiologists will be expected to interpret a significant amount of LDCT, and thus to classify numerous screen-detected PN, whose adequate management relies on their sizing and characterization. This practice is highly time consuming and subjected to both intra- and inter-observer variability. In this setting, quantitative imaging (e.g., radiomics) and artificial intelligence (AI) might have a potential in LCS optimization, allowing a faster and objective LDCT evaluation (84). Ciompi *et al.* observed a good performance of a deep learning software in nodule classification, showing how its variability was in the same range of four experienced human observers (85). The application of such approaches may also lead to a deeper nodule characterization, revealing biological features otherwise left undiscovered. Indeed, radiomics analysis consists in the extraction of imaging features undetectable to human eyesight that might reflect nodule biological behavior (86), and that can be integrated with demographics, clinical, histologic and/or genomic data.

To conclude, the integration of AI and quantitative imaging techniques in LCS will likely lead to time and resources optimization, as well as to a more precise and reproducible nodule characterization, contributing to improve patients' life quality and expectancy.

Table 2 Summary of strategies used by the LCS trials for management of solid and sub-solid nodules

Screening trial	Indeterminate	Positive
NLST (31)	Important findings not suspicious for lung cancer but requiring some form of clinical follow-up	Noncalcified nodule ≥4 mm, lung consolidation or obstructive atelectasis, nodule enlargement, and nodules with suspicious changes in attenuation
NELSON (36)	Prevalent nodule 50–500 mm^3 or incident 15–50 mm^3 was followed by LDCT after 3 months; VDT between 400 and 600 days was followed by annual LDCT; Incident nodule 50–500 mm^3 was followed by LDCT after 6–8 weeks	Prevalent nodule >500 mm^3; VDT <400 days
DLCST (22)	Nodule 5–15 mm followed by LDCT after 3 months	Nodule >15 mm or suspicious morphology; Growth >25%
MILD (76)	Prevalent 60–250 mm^3 or incident nodule 1–250 mm^3 followed by LDCT after 3 months	Prevalent or incident nodule >250 mm^3
UKLS (81)	Prevalent nodule 15–49 mm^3 followed by LDCT after 1 year; prevalent nodule 50–500 mm^3 followed by LDCT after 3 months	Prevalent nodule >500 mm^3; VDT <400 days
LUSI (14)	Prevalent or incident nodule 5–7 mm followed by LDCT after 6 months; prevalent or incident nodule 8–10 mm followed by LDCT after 3 months; prevalent or incident nodule >10 mm not highly suspicious followed by LDCT after 3 months; VDT 400–600 days followed by LDCT after 6 months (<7.5 mm); or 3 months (7.5–10 mm)	Highly suspicious; nodule >10 mm with VDT 400–600 days; VDT ≤400 days
ITALUNG (15)	Prevalent nodule 5–7 mm followed by LDCT after 3 months; incident nodule ≤3 mm followed by LDCT at 6 months; incident nodule 3–5 mm was followed by LDCT at 3 months; incident nodule >5 mm was followed by LDCT at 1 month	Persistent ≥8 mm; nodule growth ≥1 mm in consensus
DANTE (82)	Prevalent smooth ≤10 mm or non-smooth <6 mm followed by LDCT after 3, 6, and 12 months; prevalent smooth 10–20 mm or non-smooth 6–10 mm followed by LDCT after 6–8 weeks	Prevalent nodule ≥20 mm; no regression of prevalent smooth ≥10 mm or non-smooth 6–10 mm

LCS, lung cancer screening; LDCT, low dose computed tomography; VDT, volume doubling time.

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