Lung nodules: size still matters

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ABSTRACT The incidence of indeterminate pulmonary nodules has risen constantly over the past few years. Determination of lung nodule malignancy is pivotal, because the early diagnosis of lung cancer could lead to a definitive intervention. According to the current international guidelines, size and growth rate represent the main indicators to determine the nature of a pulmonary nodule. However, there are some limitations in evaluating and characterising nodules when only their dimensions are taken into account. There is no single method for measuring nodules, and intrinsic errors, which can determine variations in nodule measurement and in growth assessment, do exist when performing measurements either manually or with automated or semi-automated methods. When considering subsolid nodules the presence and size of a solid component is the major determinant of malignancy and nodule management, as reported in the latest guidelines. Nevertheless, other nodule morphological characteristics have been associated with an increased risk of malignancy. In addition, the clinical context should not be overlooked in determining the probability of malignancy. Predictive models have been proposed as a potential means to overcome the limitations of a sized-based assessment of the malignancy risk for indeterminate pulmonary nodules.

Introduction: the "size" of the problem

By definition, a lung nodule is a rounded or irregular opacity, which may be well or poorly defined, measuring ⩽3 cm in diameter, surrounded by aerated lung on radiological imaging [1]. The definition includes nodules in contact with pleura and excludes those associated with lymphadenopathies or pleural disease [2]. An opacity <3 mm should be referred to as a micronodule [1].

With the introduction of multidetector computed tomography (MDCT), the number of detected lung nodules, particularly those small in size, has dramatically increased. The prevalence of noncalcified lung

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nodules has been reported as 33% (range 17–53%) and 13% (range 2–24%), in a screening and nonscreening study population, respectively [2]. Notably, screening studies include asymptomatic subjects at high risk of developing lung cancer, among whom the majority have small noncalcified lung nodules on thin-section MDCT [3], while in a nonscreening population a lung nodule represents an incidental finding.

Since the increase in the detection rate of small pulmonary nodules, the clinical significance of these findings represents a new challenge [2, 4], and the optimal management of each case becomes pivotal and should be conducted according to the clinical setting.

After detecting a lung nodule, the main goal for physicians is to identify a nodule suspicious enough to warrant further testing as early as possible, but avoiding unnecessary diagnostic or therapeutic procedures. In cases of malignant nodules, the early diagnosis of lung cancer could provide a safe and definitive solution. In this context, detection and follow-up using computed tomography (CT) play an important role, even though the risk of false-positive results, as well as the biological cost in terms of radiation burden from several CT scans required during follow-up and healthcare costs should all be taken into account [4].

Nodule size and growth rate remain the most widely used predictors to assess probability of nodule malignancy and to determine nodule management according to the international guidelines [2, 4–7]. Indications included in the guidelines are based on the existence of a directly proportional relationship between the initial size, growth rate and risk of malignancy of nodules.

Until now, nodule management has been based on the measurement of nodule diameter, even though the more recent guidelines introduced nodule volume as an indicator. The British Thoracic Society (BTS) added initial volume and volume doubling time (VDT) calculations to the diameter, and the Fleischner Society added volume [2, 7]. The data on volumetry are mainly derived from the Dutch–Belgian Lung Cancer Screening trial (NELSON) evidence [8].

When considering size for managing an indeterminate pulmonary nodule the existence of a potential inherent inaccuracy of nodule measurements in terms of diameter, volume and growth rate should be taken into account.

In this review we debate the relevance of size and growth rate in nodule characterisation, as well as the currently used methods for measuring pulmonary nodules, their limitations and factors influencing nodule measurement variations and growth estimation. Special considerations on subsolid nodules (SSNs) are included in this context. Finally, the risk prediction models that integrate clinical and nodule characteristics besides size and the role of nodule size as a factor affecting the critical time for follow-up are briefly discussed.

Size and malignancy

In the above-described scenario, a strong effect of the nodule size on predicting malignancy has been underlined, even though the management of a pulmonary nodule cannot solely rely on size.

It has been widely demonstrated that there is a proportional increase in the risk of malignancy as the nodule diameter increases, as reported in an extensive review [9]. McWilliams *et al.* [10] confirmed the observation that nodule diameter is associated with lung cancer probability, with a significant nonlinear relationship in patients undergoing low-dose CT screening ($p<0.001$ for nonlinearity).

It is worth noting that the prevalence of malignancy in nodules measuring <5 mm is very low, ranging between 0 and 1% [8, 9]. In the National Lung Screening Trial (NLST), the prevalence of lung cancer among patients with 4–6-mm nodules was very low: 0.49% (18 out of 3668 patients) at baseline, 0.3% (12 out of 3882 patients) in the first screening round and 0.7% (15 out of 2023 patients) in the second round of screening [11, 12]. Moreover, in the NELSON study malignancy risk in subjects with nodules measuring <5 mm or <100 mm^3 was similar to the risk in subjects without nodules [8]. By taking into account these observations, according to the recent guidelines the nodule size threshold (diameter or volume) for determining the need for follow-up has been increased to 5 mm or 80 mm^3 for BTS guidelines and 6 mm or 100 mm^3 for Fleischner Society guildeines [2, 7].

In table 1 we summarise the relationships between the diameter of pulmonary nodules and the prevalence of malignancy, as reported in a large literature review [9], and between diameter, volume and VDT with the prevalence of malignancy as reported in the NELSON screening study by Horeweg *et al.* [8].

Apart from nodule size, it is well known that nodule appearance in terms of density affects the probability of malignancy, reflecting histological differences between lesions.

TABLE 1 Relationship between nodule size, expressed as diameter and volume, and growth rate, expressed as volume doubling time (VDT), with the prevalence of malignancy

	Prevalence of malignancy %	
	NELSON screening study [8]	**Literature review [9]**
Diameter mm		
<5	0.4	0–1
5–10	1.3	6–28
⩾10	15.2	33–60
⩾20		64–82
Volume mm^3		
⩽100	0.6	
100–300	2.4	
⩾300	16.9	
VDT days		
⩾600	0.8	
400–600	4	
⩽400	9.9	

Data from [8, 9].

Data from the literature confirmed the above-described relationship between nodule size and malignancy even when distinguishing lung nodules according to their density. The first screening trials demonstrated a ⩽1% malignancy risk in solid nodules <5 mm in diameter, as reported in the Early Lung Cancer Screening Project (ELCAP), and in the Mayo Clinic CT screening trial the majority (80%) of cancers were >8 mm in diameter [13–15].

Regarding SSNs, including pure ground-glass nodules (pGGNs), named nonsolid nodules and part-solid nodules (PSNs), results derived from the ELCAP [14] and the following I-ELCAP screening studies [16, 17] demonstrated a prevalence of malignancy for small nodules of 0% (considering a maximum nodule diameter of 5 mm) and <1% (considering a maximum nodule diameter of 6 mm). In both experiences an increase in malignant cases was associated with an increase in nodule diameter [14, 16, 17]. Furthermore, in the early ELCAP screening the prevalence of malignancy was higher among SSNs, particularly when considering PSNs (18% for pGGNs and 63% for PSNs), than among solid ones (7%) [14].

Therefore, it has been suggested that for SSNs, management and T staging assessment, as included in the tumour node metastasis classification, should be adjusted by measuring both the overall nodule size and the solid component size [6, 18, 19].

Size changes: the growth rate

Small nodules are not reliably characterised by contrast enhancement evaluation or positron emission tomography scanning and biopsy is difficult to perform on these nodules. However, the risks involved in a surgical diagnosis would be excessive compared to the relatively low prevalence of malignancy in the small nodules.

Nodule growth, determined by imaging surveillance, could be used as a diagnostic tool for assessing malignancy [5]. By performing an "early" repeated CT within 30 days, Yankelevitz *et al.* [20] accurately detected growth in nodules as small as 5 mm and Zhao *et al.* [21] demonstrated that the majority of resolving nodules disappeared at the same time point.

Collins *et al.* [22] advanced the theory of an exponential growth of tumours to predict the growth rate, which assumes a uniform three-dimensional (3D) tumour increase. Therefore, growth is typically expressed in terms of VDT, defined as the time taken for the nodule to double in volume or to increase 26% in diameter [5, 22].

Lindell *et al.* [23] analysed the growth curves of lung cancer detected in a screening population, observing that lung cancers may be associated with a fairly steady or accelerated growth, particularly the more aggressive tumours. The authors concluded that the initial tumour size at one point and the interval growth assessed between two points are not predictive of the future growth, therefore the likelihood of a nodule to be malignant may be misinterpreted by using models assuming an exponential growth [23].

Interesting results have been reported on VDT by Xu *et al.* [24], who retrospectively investigated the role of morphological features, size and VDT in the differentiation between benign and malignant lung solid

nodules detected in the NELSON trial. The study demonstrated that by using a multivariate model, when follow-up data are available, nodule growth assessed by VDT at 1-year follow-up was the only strong predictor for malignancy.

A wide range of growth rates for lung cancer has been reported in literature, according to different methods used to measure the nodule (diameter, manual bidimensional or automated 3D volume), as well as to the histological subtypes and radiological appearance [2]. The clinical setting seems not to affect the nodule growth rate, in fact no significant differences between screening and nonscreening studies have been demonstrated in this regard [25].

VDTs in the range of 20–400 days have been reported for malignant solid nodules, with a 98% negative predictive value of malignancy for a VDT of >500 days (calculated using volumetric software) [26]. Longer times have been considered for malignant SSNs, in particular 813±375 days and 457±260 days for pGGNs and PSNs, respectively [2, 25–30]. Notably PSNs with a solid component ⩽5 mm showed significantly longer VDT, compared to lesions with a solid portion >5 mm [31].

In the NELSON screening trial, growing nodules were stratified in risk groups according to VDT (high risk <400 days; intermediate risk 400–600 days; low risk >600 days) [32]. Specifically, VDT stratified the probabilities of malignancy as follows: 0.8% (95% CI 0.4–1.7%) for VDT ⩾600 days, 4.0% (95% CI 1.8–8.3%) for VDT 400–600 days and 9.9% (95% CI 6.9–14.1%) for VDT ⩽400 days [32].

Size measurements: methods and limitations

Size measurements of lung nodules need to be accurate and precise to allow correct risk classification and to assess changes in nodule size over time. Accuracy describes the difference between the mean value of the object measured and its true value [33]. Precision refers to variability in performing different measurements on the same experimental unit, when measurement setting is either stable or variable [33]. These characteristics are particularly relevant for small-sized nodules whose changes, even when doubled in time, are difficult to recognise visually.

Lung nodules can be evaluated according to diameter, area or volume, calculated either by manual or semi-automated/automated methods. Semi-automated methods allow the operator manual interaction with the automated modality.

Results from the literature agree that volume measurement is a method with a better performance in nodule sizing, as well as in assessing nodule's growth [34, 35]. Mehta *et al.* [36] added volumetric nodule measurement to an existing prediction model for nodule malignancy estimation, showing an increase in the number of nodules correctly classified. Notably, the study included only lesions <15 mm in diameter. A more recent study on lung cancer probability applied to the NELSON population compared nodule management strategies based on nodule volume (cut-offs 100 mm^3 and 300 mm^3 for an indeterminate and a positive test, respectively) *versus* nodule diameter (cut-offs 5 mm and 10 mm for an indeterminate and a positive test, respectively) [37]. The study concluded that the volume-based analysis had a sensitivity and negative predictive value comparable to those resulting from the diameter-based analysis, whereas the specificity and positive predictive values were higher [37].

In this context technical and practical issues need to be considered. Firstly, nodule diameter measurement is not a reliable method for assessing the entire nodule dimension and it is affected by non-negligible inter- and intra-observer variability. Secondly, volume measurement methods tend to be more susceptible to the influence of technical parameters and software type used to perform volumetry. Moreover, automated systems are not routinely used, mainly because they usually are not integrated in the picture archiving and communication system [38] and their application may be time consuming.

One-dimensional and two-dimensional measurements

The most commonly used method to define nodule size consists in measuring the maximum nodule diameter using a one-dimensional (1D) calliper, according to the RECIST (Response Evaluation Criteria in Solid Tumours) criteria [39]. This method has been promoted as a more practical and simple system than that of the World Health Organization [39]. Established in the late 1970s, the latter relies on two-dimensional (2D) or cross-sectional area measurement, calculated by multiplying the tumour's maximum diameter in the transverse plane by its largest perpendicular diameter on the same image [39]. Interestingly, the 2D measurement showed a greater variability when applied to solid nodules compared to 1D and volumetric methods [40]. Moreover, as reported by Jennings *et al.* [34], in the assessment of growth the use of the cross-sectional area did not perform significantly better than the diameter.

Another method of measuring nodule size is to assess the average diameter, calculated between the maximal long-axis and perpendicular maximal short-axis diameters assessed on transverse CT sections.

This method has been recommended by the Fleischner Society in the guidelines published in 2005 and 2013 for management of indeterminate pulmonary nodules, as it reflects the entire nodule dimensions more accurately [4, 6].

There are some limitations of these methods affecting both accuracy and precision of nodule measurements. When using 1D or 2D measurements we consider only the subset of data included in the maximum cross-sectional diameter or area measured on the axial image [41]. It is worth noting that the maximum nodule diameter may be in nonaxial images (figure 1a and b).

Errors and variability are particularly evident when considering small nodules. In a retrospective analysis including only solid noncalcified pulmonary nodules <2 cm in diameter, Revel *et al.* [42] stated that the largest transverse cross-sectional nodule diameter manually measured by positioning an electronic calliper is not reliable due to a poor intra- and inter-reader agreement (figure 1c and d). The best intra-reader repeatability coefficient (5% error rates) was 1.32 and the 95% limits of agreement for the difference among readers was ±1.73 [42]. From a clinical point of view, this means that by using the 1D method, measurement values <1.32 and <1.73 mm cannot be distinguished from errors.

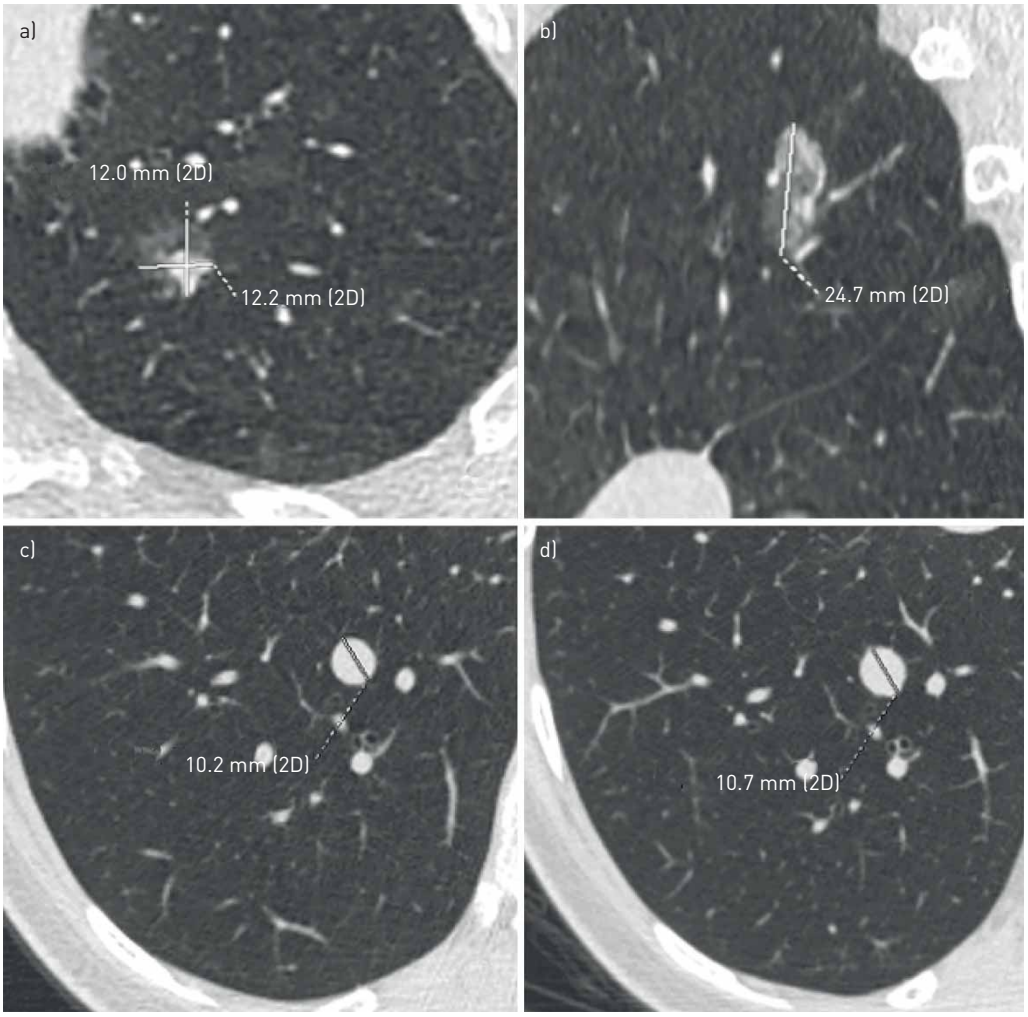

FIGURE 1 Limitations of two-dimensional (2D) measurements. The axial diameter may not be the maximum one in the evaluation of lung nodules. a) A small part-solid nodule in the apico-posterior segment of the left upper lobe, with a maximum axial diameter of 12×12.2 mm; b) the sagittal multiplanar reconstruction shows that the largest diameter of the same nodule is the sagittal one of 24.7 mm. The multiplanar evaluation of nodule diameter is especially important to document asymmetrical growth of nodules. c), d) The low level of agreement when measuring small nodules: for the same nodule in the right lower lobe two different diameter values have been reported by two readers. Considering the nearest whole diameter of the two values, it results in 1 mm difference in the maximum diameter, a significant difference when considering small nodules.

Furthermore, a study derived from NLST demonstrated that variations in 1D measurement of pulmonary nodule diameter performed using electronic calliper account for much of the disagreement among readers in the classification of the screening results as positive or negative, in particular when considering nodules with irregular shape and indistinct margins [43].

In the attempt to reduce variability in nodule measurements, the latest version of the Fleischner Society guidelines published in 2017 recommended the calculation of the average nodule diameter between the long and the short axis in whichever plane (axial, coronal or sagittal) the nodule shows its maximum dimension [7]. A following statement focused on recommendations for measuring pulmonary nodules clarified that for nodules <1 cm the dimension should be expressed as average diameter, while for larger nodules both short- and long-axis diameters taken on the same plane should be reported [44].

With regard to SSNs, visual evaluation is a difficult task as nodule margins tend to be ill-defined and have a low contrast with respect to the surrounding lung parenchyma. In this context, uncertainties exist not only in the nodule measurement, due to difficulties in delineating nodule margins and different densitometric components of PSNs, but also in the classification of nodule morphological characteristics (*i.e.* pGGN or PSN) [45, 46].

For SSNs a maximum variability of ±2.2 mm in measuring both the longest nodule diameter and the average one has been reported [46]. The recent BTS guidelines corroborated these data and stated that for SSNs an increase in the maximum diameter ⩾2 mm is strongly predictive of malignancy [2]. When considering small SSNs (<1 cm) the variability in measuring nodule dimension was lower when using the average diameter than the longest one [46]. The latest statement from the Fleischner Society on nodule measurements supports this evidence and recommends the expression of the dimension of SSNs <1 cm as average diameter, as for solid nodules [44].

Two recent studies focused on the evaluation of observer variability in visual classification of SSNs and the potential implication on patient management, both in a screening and nonscreening setting [45, 47]. Agreement values were moderate (intra- and inter-observer agreement κ-values of 0.57 and 0.51, respectively in the screening setting; inter-observer agreement κ-value of 0.56 in the nonscreening setting) and discordance in nodule classification was mainly due to the assessment of the solid component, in terms of presence and size [45, 47]. This variability is probably related to the lack of standardised criteria on how to measure different densitometric components of SSNs and on which CT window setting (*i.e.* lung or mediastinal) should be used, at the time of their publication.

A recent article demonstrated that the lung window setting has a comparable reproducibility, but higher accuracy in SSN classification and measurement of the solid component than the mediastinal window setting [48]. Moreover, Lee *et al.* [49] showed that the size of a solid portion displayed at the lung window setting better correlates with the nodule invasive component. Conversely, by using a mediastinal window setting, only areas >−160 Hounsfield units can be detected as solid, resulting in an underestimation of the size of the solid portion (figure 2) [45, 46]. Therefore, on the basis of the updated literature, recommendations from the Fleischner Society suggest the use of the lung window setting and the high spatial frequency (sharp) filter to judge the presence of a solid component, and the measurement of both the solid and nonsolid portions in a PSN. The same display window setting is recommended for measuring solid nodules [44].

3D measurements

The most commonly reported 3D methods for nodule volume measurement are those performed using manual or semi-automated/automated techniques.

When measuring volume manually, the region of interest (ROI) is first defined by outlining the 2D nodule borders section by section and then applying 3D software that estimates nodule volume from the number of voxels included within the multiple ROIs [50].

By using semi-automated/automated methods the ROI is defined automatically or by starting from a point inside the nodule selected by the user. Afterwards a segmentation algorithm is applied to outline 3D nodule borders and calculate the volume. Segmentation is often based on a threshold density technique followed by voxel counting for the volume estimation. Alternative methods include the estimation of the nodule shape in the continuous space of the object [50].

One of the first applications of volumetric analysis was the study by Yankelevitz *et al.* [41], who compared the accuracy of 3D techniques in determining volume with the accuracy of 2D techniques in defining a cross-sectional area. On synthetic spheres volume estimation was reliable as the area measurement and, moreover, the VDT estimated on *in vivo* nodules appeared to be more consistent with the final pathologic diagnosis, as opposed to 2D techniques [41].

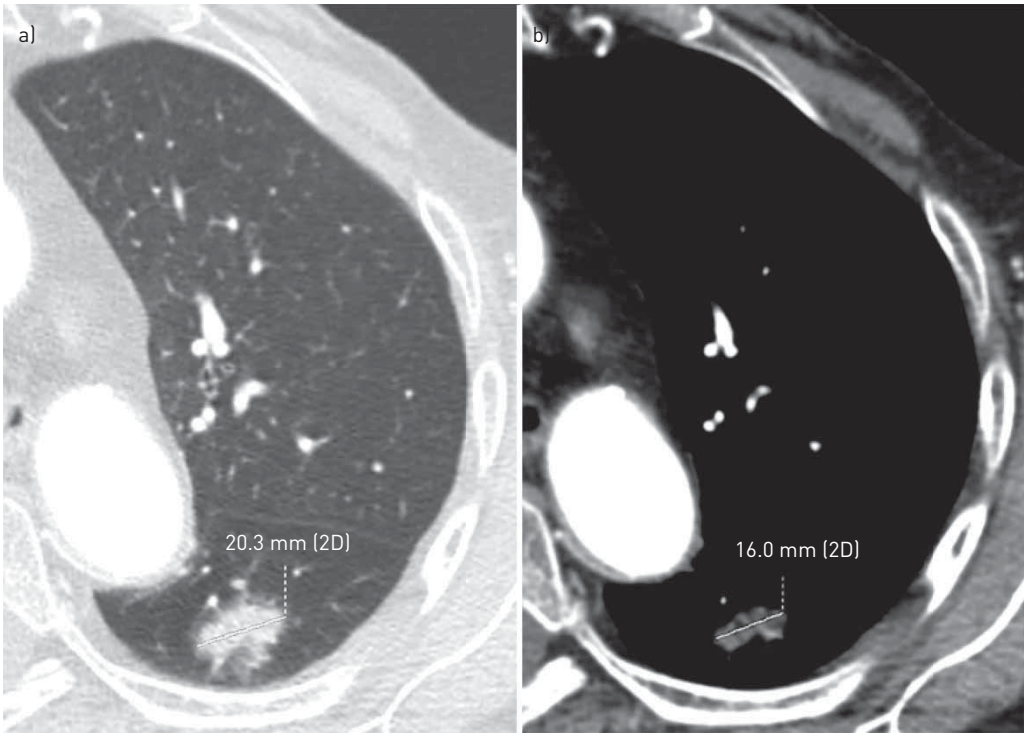

FIGURE 2 Disagreement in measuring the solid portion of a part-solid nodule when using different reconstruction algorithms and window settings. A part-solid nodule in the apical segment of left lower lobe is shown. a) By using a high-spatial frequency algorithm and the lung window, the measured maximum axial diameter of the solid portion of the nodule corresponds to 20.3 mm; b) by using a smooth algorithm and the mediastinal window, the measured maximum axial diameter of the solid portion of the nodule corresponds to 16 mm. 2D: two-dimensional.

In a preliminary experience with nodule 3D evaluation, Revel *et al.* [51] reported a maximum measurement error of 6.38% (upper limit of the 95% limit of acceptability) and underlined that a 6.38% increase in volume corresponds to a 2.1% increase in diameter (*e.g.* 0.1 mm and 0.2 mm for nodules measuring 5 mm and 10 mm, respectively). Therefore, the precision of the 3D method can be considered to be much higher than that of the manual method of measuring diameter.

Moreover, high intra- and inter-reader agreement has been reported in the literature for volumetry (up to 0.99) [52–55], and volumetry performance was independent from the observer experience [55].

Factors influencing nodule measurement variations

The performance of 1D and 2D measurements depends mainly on nodule size, technical conditions and reading setting.

As regards size, major concerns exist in the measurement of small nodules. By using a field of view of 360 mm and an electronic matrix of 512×512, as is commonly applied in chest CT scan acquisition, the pixel dimension is ~0.7 mm [56]. Therefore, a small difference in calliper positioning, even of a single pixel, could result in a significant difference in nodule size.

Regarding technical issues, nodules are better detected and characterised using thin and contiguous CT sections, as confirmed by results in the literature [2, 57–61]. It has been well established that contiguous thin-section CT scans reduce the partial volume effect that is responsible for errors in nodule margin delineation and in density recognition. In particular, it has been suggested that thin-section images increase sensitivity in detecting pGGNs and avoid the misinterpretation of solid nodules as SSNs [60]. Another parameter affecting accuracy in nodule measurement is the low tube current applied to perform CT scans, particularly in the screening programmes. The intrinsic increase in image noise of low-dose CT images may simulate the presence of a ground-glass opacity or may hide the margins of a pGGN, thus resulting in lesion misinterpretation and inaccurate measurement [60–62].

In addition, image reading settings may play an important role in assessing nodule size, particularly in the follow-up. Lower variability in lesion sizing has been reported when readers have the chance to consult

previous measurements as compared to an "independent" reading session performed without any baseline measurement [63]. Furthermore, nodule size assessment performed during follow-up by the same radiologist and using automated software to compare images is helpful in reducing measurement variations, particularly as regards GGNs, for which subtle changes in size and density may be better underlined [64].

The accuracy and precision of 3D nodule volume measurement are influenced by multiple factors related to nodule/patient characteristics and technical issues.

Regarding nodule characteristics, volume overestimation of the small nodules due to the partial volume effect represents quite a challenge. It is a common imaging artefact when a limited spatial resolution is used to perform CT scans and, consequently, different tissues are included in the same pixel/voxel [50, 52, 65–69]. When attenuation value is not sufficient to distinguish nodule borders, segmentation errors could occur, as in the case of nonspherical or irregular lesions [41, 65, 68, 70–72], as well as in juxtavascular or juxtapleural ones [72–74]. Reduced nodule attenuation, as in the case of SSNs, could also affect nodule segmentation when using the commonest threshold density technique, because of the low attenuation difference between nodule borders and the surrounding parenchyma [50]. Moreover, in PSNs the ground-glass component, usually peripheral, may hinder software detection of attenuation differences with the surrounding parenchyma, even for the solid portion [75]. Earlier studies described significantly higher errors of volumetry when evaluating SSNs in comparison to the solid nodules [76] and low correlation of volumetric assessment of the solid component (calculated as ratio of the solid component to the whole volume) with the histopathological classification [77]. Thanks to the development of specific software, volumetric measurement of SSNs has become accurate over the years with a successful segmentation of up to 97% of the nodules [75, 78–80]. Similar results have been reported in the detection and segmentation of PSNs and, interestingly, a quantification of the solid component was related to pathological prognostic factors, such as lymphatic, vascular and pleural invasion [75, 81, 82].

As regards patient characteristics, cardiovascular motions affect volumetry because they are conveyed to lung parenchyma and determine changes in the volume of pulmonary nodules, especially the smallest ones [83]. Conflicting results are reported in the literature regarding the effect of respiratory phases on lung volume and, as a consequence, on the nodule volume measurement. Some authors showed an inverse relationship between inspiratory effort and nodule volume [84, 85], while others did not [65]. It should be kept in mind that CT volumetric measurements of SSNs, regarding both the ground-glass and solid components, showed a tendency to be larger than the histological counterpart, because of the different inflation state of the lung applied to a focal soft tumour [49, 78].

There are several technical factors affecting nodule volume estimation, such as section thickness [40, 68, 69, 86–89] and overlapping [90, 91], pitch mode [92], reconstruction algorithm [86, 89–91, 93–95] and intravenous contrast medium injection [95–97], as summarised in table 2. In addition, major technical concerns exist regarding nodule volumetry during follow-up. First, different performances are reported when using different scanner types [50, 86, 98]. Secondly, volumetry is affected by variability in the segmentation process due to differences in the method and software used. The automated method can introduce biases in volume measurements due to a different software performance, even though it has been demonstrated that it reduces observer variability [113, 114]. Manual correction it is expected to act on these biases [55, 115]. Differences in volume estimation have been reported when using different software and different algorithms of correction of partial volume effect artefacts [57, 67, 116–118]. Therefore, it is advisable to perform nodule follow-up using the same scanner, technique and software package.

Another relevant issue is the potential influence of tube current on volumetry. Few experiences reported a low performance of volumetry due to tube current reduction [76, 99, 100]. A larger number of results derived from studies using newer generation scanners did not confirm the previous observations. Indeed, the introduction of iterative reconstructions, employed to increase image quality in favour of a further reduction of the effective radiation dose, demonstrated an even better performance compared to that of the traditionally used filtered-back projection reconstructions [101–112].

Effect of measurement variations on nodule growth

If we keep in mind the aforementioned exponential model of nodule growth, small change in nodule dimension may be clinically relevant. By using 1D and 2D methods small changes in nodule dimension may not be detected, resulting in a low sensitivity in identifying potential malignant lesions [42]. Furthermore, it has been demonstrated that growth assessment based on the maximum diameter measurement in noncalcified lung nodules, classified as positive at NLST, results in a moderate agreement among readers (κ=0.55) with potential implications in patient management [119]. In the same way,

TABLE 2 Technical factors that may affect volume measurement

	Effects on volumetry
Section thickness	Volume overestimation with thick sections [40, 68, 69, 86–89]
Overlapping reconstruction	Volume overestimation with non-overlapping sections [90, 91]
Pitch	Low accuracy with high pitch mode [92]
Reconstruction algorithms	Easier nodule sampling with high spatial frequency algorithms [86, 89, 91, 93]
	Volume overestimation with high spatial frequency algorithms [90, 94, 95]
Intravenous contrast medium	Volume overestimation [95–97]
Scanner type	Differences in volume estimation [50, 86, 98]
	Higher accuracy with helical CT scanner [98]
Low radiation dose	Low accuracy [76, 99, 100]
Iterative reconstruction	Better performance [101–112]
Manual *versus* semi/automated method	Reduced observer variability with automated system [113, 114]
	Manual interaction reduces bias due to the software performance [55, 115]
Software and algorithms package	Differences in volume estimation [57, 67, 116–118]

CT: computed tomography.

relative errors have been reported when manually measuring 1D longest diameters according to the RECIST criteria to evaluate response to treatment of lung metastases [120]. These errors, when using 1D and 2D measurements, can lead to a big difference in estimating growth rate, considering the multiplier effect when volume and doubling time are estimated on the basis of diameter [42, 120].

Growth is a 3D phenomenon, therefore an asymmetrical growth could not be detected by using 1D or 2D methods, especially if it occurs in a different plane with respect from the axial one [41]. Intuitively, the direct assessment of nodule volume and VDT provides an accurate estimation of nodule growth [51]. Combined with lower uncertainty of measurements, the 3D method allows detection of changes even within a shorter period of time, resulting in a higher sensitivity of volume-based techniques in growth evaluation [26, 73] (figure 3). Estimations of nodule growth rates obtained from automated 3D volumetric measurements showed a good correlation with 2D diameter measurements, with a greater divergence for irregular lesions [70]. Since all the available data are included in the nodule volume definition and calculation, irregular nodules are evaluated with small magnitude errors and asymmetric growth could be reliably defined by using volumetric methods [41]. However, the reported volume measurement errors vary between 20% and 25%, therefore a change in volume of ⩾25% should be considered to define a significant growth [2, 33, 121]. In the screening setting, Marchianò *et al.* [122] reported similar values of repeatability, with the 95% confidence interval for the difference in measured volumes of ±27%.

Subsolid nodules: special considerations

When evaluating SSNs, nodule density provides major and additional information in terms of malignancy prediction.

While the proportion of ground-glass opacity was found to be a significant prognostic factor of less invasive cancer, the presence of a solid component corresponds to the pathological finding of tumour invasion and, therefore, represents a predictor of malignancy [2, 6]. Particularly in PSNs, a smaller solid portion has been described as an independent differentiator of a pre-invasive lesion from an invasive adenocarcinoma [123] and, moreover, the diameter of the solid component has a better correlation with patient prognosis than the whole-lesion diameter [18, 124]. Finally, some typical radiological patterns, in terms of both nodule size and density, could be related to different histological categories described in the latest adenocarcinoma classification: the two premalignant (atypical adenomatous hyperplasia) and pre-invasive (adenocarcinoma *in situ*) lesions usually appear as pGGNs with a diameter of <5 mm or >5 mm, respectively; minimally invasive adenocarcinoma as a PSN with a solid area <5 mm; and invasive adenocarcinoma as a larger PSN or solid nodule [2, 124, 125].

Some studies have tried to identify a "threshold size" of different densitometric components in relation to nodule malignancy. Nodules with a ground-glass component of >50% showed a significantly better prognosis [126]. In PSNs, Lee *et al.* [49] observed that a maximum diameter of the solid component of ⩽3 mm was predictive of a pre-invasive or minimally invasive histology and two volumetric measurements (solid volume ⩾1.5 cm^3; percentage of solid volume ⩾63%) were found to be independent indicators

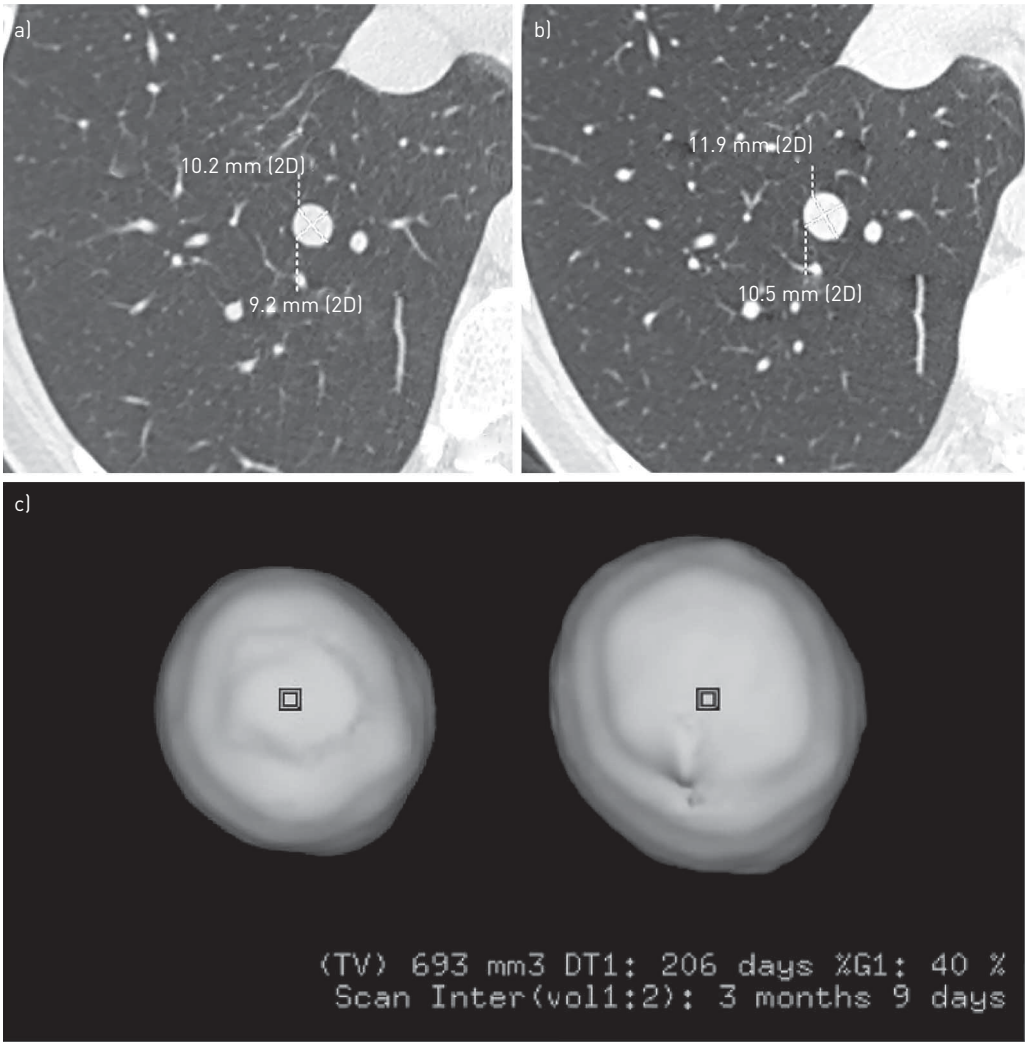

FIGURE 3 Volume evaluation during follow-up allows the detection of nodule growth over a shorter period of time compared to diameter estimation. a) Computed tomography (CT) axial image shows the same nodule located in the right lower lobe as reported in figure 1c; b) a 3-month follow-up axial CT image demonstrates minimal change in nodule diameters; c) conversely, nodule volume calculation using a three-dimensional (3D) volumetric method demonstrates a significant increase in volume within the range of malignancy. Histopathology revealed a carcinoid tumour. 2D: two-dimensional; TV: total volume; DT: volume doubling time; %G: volume increase; scan inter: scan interval. Squares in the nodule represent the starting points of the 3D analysis.

associated with increased likelihood of recurrence and/or death in patients with stage I adenocarcinoma [127]. Likewise, the ratio of the solid component to total tumour is related with tumour histology and therefore is a useful method of estimating prognosis [128, 129].

To reflect the changes in SSNs, not only in size but also in attenuation, another approach has been proposed, *i.e.* the estimation of the mass that integrates the nodule volume and density [130]. In a clinical evaluation, DE HOOP *et al.* [131], when applying nodule mass assessment (*i.e.* mean CT attenuation × volume) demonstrated a smaller measurement variability compared with diameter and volume and an earlier detection of nodule growth. Notably, the latter is due to a better capability of detecting the appearance or progression of a solid component in SSNs [131]. The usefulness of the system has been proven afterwards by other experimental studies [78, 81, 132] and used in the discrimination of histological subtypes in adenocarcinoma [133]. As for volumetric measurement, an existing interscan variability has been described for nodule mass assessment, and an increase in nodule mass of 30% has been regarded as a significant growth [134].

To corroborate the prognostic significance of nodule density in SSNs in terms of clinical decision making, the Fleischner Society recommendations for managing incidental SSNs categorised nodule risk on the basis of nodule density and not only on size and growth [6, 7].

Similarly, the American College of Radiology published the Lung CT Screening Reporting and Data System (Lung-RADS) in 2014 [135], a scoring system that considered nodule density, in addition to size and growth, as relevant predictor of malignancy to categorise screening-detected lung nodules. The classification from 1 to 4X categories corresponds to an increasing risk of malignancy. Category 4X is assigned to nodules with additional imaging features requiring a more intensive diagnostic work-up [135].

The added value of the Lung-RADS category 4X in the differentiation of benign and malignant nodules has been evaluated for SSNs in a recent study by Chung *et al.* [136]. Six experienced chest radiologists were asked to analyse the characteristics of 374 SSNs in the NLST database that would have been classified as category 3, 4A, and 4B according to the Lung-RADS system. The radiologists indicated which nodules were suspicious and that they would hence raise the Lung-RADS category to 4X. In addition, the readers indicated which imaging characteristics made them upgrade the nodule to 4X. Results demonstrated that the malignancy rate derived by adding morphological criteria (*i.e.* internal structure, presence of bullae, solid core characteristics, borders and surrounding tissue features) is superior to the risk assessed only on nodule type and size, with an average rate of malignancy of 53% with respect to the generic rate assigned by conventional Lung-RADS to the 4X category (>15%) [136].

This observation emphasises the concept that the assessment of SSN characteristics by an expert radiologist outperforms the evaluation based only on nodule size and type in predicting malignancy.

Integrating clinical and nodule characteristics: risk prediction models

Several predictors of malignancy have been identified in a number of studies that reported multivariate analyses. When evaluating individuals with lung nodules, the probability of malignancy is estimated on the basis of patient-related clinical factors and nodule characteristics, including size [2, 4–6]. Among the clinical factors, older age, heavy current/former smoker, exposure to other inhaled carcinogens (asbestos, radon or uranium), as well as the presence of emphysema or fibrosis and family history of lung cancer have been demonstrated to be predictors of malignancy, as reported in the latest review of the Fleischner Society guidelines for nodule management [7]. As regards nodule morphological characteristics, besides small size, diffuse, central, laminated or popcorn calcifications, as well as fat tissue density and perifissural location have been recognised as indicative of benign lesions. In contrast, a large nodule diameter, or the evidence of nodule spiculation, upper lobe location, pleural indentation and VDT <400 days have been consistently identified as factors related to a higher risk of malignancy [2].

Some of these determinants have been included and tested in composite prediction models, developed with the scope to assist clinicians in the difficult task of nodule characterisation [3, 10, 137]. Currently the American College of Chest Physicians guidelines suggest using the Mayo Clinic prediction model based on patient categorisation into low (>5%), intermediate (5–65%) and high risk (>65%) of malignancy [5], while the BTS guidelines suggest the use of the Brock and Herder models [2]. More recently, the Bayesian inference malignancy calculator model proved to be an accurate tool for characterising pulmonary nodules by guiding lesion-tailored diagnostic and interventional procedures during work-up [138].

In this context, it is worth mentioning that the accuracy and applicability of predictive models depend on the population in which they were derived and validated (*e.g.* screening, routine and oncology), according to differences in the prevalence of malignancy and in methods of evaluation.

Size and follow-up recommendations

The critical time for surveillance is the earliest point at which the nodule growth can be detected. Considering nodules detected in a screening programme, Kostis *et al.* [66] described nodule size at detection as a factor affecting the critical time for follow-up CT. Similarly, in the international guidelines for the management of indeterminate nodules, time surveillance is dependent on the initial nodule size; the bigger the nodule diameter the shorter the follow-up interval time [2, 4–7]. Despite the need for early diagnosis in cases of malignant nodules, it must be kept in mind that a higher accuracy of growth rate assessment and an improvement of malignancy risk evaluation with a longer interval time between the follow-up CT scans have been described in the literature [6, 24, 70].

Some doubts remain regarding the duration of follow-up, not only because of the extremely long VDT of certain lung cancers, but also because some tumours (*i.e.* adenocarcinoma) showed a long period of stability before growing or even reducing in size during surveillance [23, 28, 139].

Nevertheless, the notion of a 2-year stability implying benignity is widely accepted in common clinical practice, specifically for noncalcified solid pulmonary nodules, and the aforementioned results from the NELSON screening trial support such practice [2, 8]. In contrast, a longer follow-up period is required for classifying for SSNs as benign with a reasonable certainty.

In the latest revised Fleischner Society Guidelines [7], which take into consideration data from the major lung cancer screening projects in Europe and United States [8, 10, 11, 16, 17, 140] a new approach has been proposed for managing incidentally identified pulmonary nodules. For solid nodules, the minimum threshold of diameter requiring follow-up has been elevated to 6 mm in order to reduce false positives, and a follow-up time range has been introduced to reduce the number of examinations performed in the stable nodules. However, a longer period before the initial follow-up has been recommended for managing SSNs, because of their indolent nature when cancerous [7]. Reports in the current literature [17, 141] state that GGNs with diameter ⩾6 mm should be followed-up for 5 years, with time scan intervals of 2 years, while PSN with a solid component <6 mm should be evaluated annually for 5 years. In the case of PSNs with a solid component ⩾6 mm, after an initial follow-up, other nodule characteristics (such as morphological features and an eventual growth) as well as the clinical setting should guide further management [7].

Conclusions

With the diffusion of lung cancer screening programmes worldwide, the "database" of small pulmonary nodules has become huge. Furthermore, MDCT has dramatically increased the number of small-sized nodules identified on thin-section images. In this context, size and growth rate still represent pivotal factors for nodule characterisation, even though some limitations in evaluating pulmonary nodules when considering only their dimensions have been recognised. Firstly, there is no univocal method for measuring nodules (diameter, area, volume or mass). Secondly, intrinsic errors, which can determine variations in measurements and affect nodule growth assessment, do exist when using 1D, 2D and 3D methods. Finally, nodule CT attenuation has become a widely accepted significant determinant of prognosis over the past few years, specifically in SSNs. More recently, in these types of nodules, other morphological features (*i.e.* internal structure, presence of bullae, solid core characteristics, borders and surrounding tissue features) have been associated with an increased risk of malignancy.

Physicians should be aware that size and its change over time remain the most important factors determining nodule management, as stated in the currently used international guidelines, even though these factors should be evaluated in relation to other nodule characteristics, without overlooking the clinical context. Therefore, predictive models that take into account several factors have been proposed as a potential means to overcome the limitations of a size-based assessment of the malignancy risk for indeterminate pulmonary nodules.

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