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REVIEW ARTICLE

Lung nodules: sorting the wheat from the chaff

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ABSTRACT:

Pulmonary nodules are a common finding on CT scans of the chest. In the United Kingdom, management should follow British Thoracic Society Guidelines, which were published in 2015. This review covers key aspects of nodule management also looks at new and emerging evidence since then.

INTRODUCTION

The number of CT scans performed in the United Kingdom (UK) is increasing year on year. Data from the Diagnostic Imaging Dataset (DID) for England showed that 679,015 CT scans of the chest and/or abdomen were performed in England between March 2021 and March 2022, a 6% increase from the preceding 12 months.[1] Pulmonary nodules are a common incidental finding. They have a prevalence of 13% (range 2–24%) in non-screening populations, which rises to 33% in those undergoing lung cancer screening (range 17–53%).[2] More than 50% of patients with a pulmonary nodule have more than one nodule.[3] A review of published data for the British Thoracic Society (BTS) guideline showed that lung cancer prevalence was similar for nodules detected across both groups at 1.5% (incidental) and 1.4% (screening).[2] A recent study from the United States examined nodules detected via screening and those from an incidental nodule management pathway. The authors showed a lung cancer detection rate of 2.7 and 4.9% respectively.[4] Importantly, many of the incidental nodule detection group would not have been eligible for screening but both groups had favourable outcomes.

Management of pulmonary nodules, whether detected by screening or incidentally, aims to maximise early detection of malignancy while minimising harms (and cost) from overinvestigation. This is particularly important given the recent positive recommendation from the United Kingdom National Screening Committee regarding screening for lung cancer with low-dose CT (LDCT) in September 2022. This paper covers some key aspects of the management of pulmonary nodules and considers new or emerging evidence since the publication of the BTS Guidelines in 2015.[2]

NODULE MANAGEMENT GUIDELINES AND STATEMENTS

Nodules should be managed according to evidence-based guidelines. There are several guidelines and statements that are available for the management of nodules, covering those detected incidentally and in the lung cancer screening setting. In the UK, the BTS Guidelines are used for both incidentally and screen-detected nodules.[2] The other main guideline covering incidentally detected nodules is from the Fleischner Society.[5] Table 1 summarises the key recommendations from these guidelines for solid and subsolid nodules (SSNs).

It is important to recognise that these guidelines may not apply to patients in whom the risk of malignancy differs from the general population, *e.g.* known or recent malignancy (within the past 5 years), organ transplant or immunocompromise, or those aged <18 years.

There are four statements/guidelines that also give guidance for nodules specifically detected via screening: the European position statement on lung cancer screening, Lung-RADS® v. 1.1 from the American College of Radiology, the National Comprehensive Cancer Network Screening Guideline v. 1 and the International Early Lung Cancer Action Program (I-ELCAP) nodule protocol.[6–9] These are particularly useful when it comes to the management of incident (new) nodules. Lung-RADS® v. 1.1 is the one most widely used in United States lung cancer screening programs and also adopted in several other countries that are running screening pilots. In the latest update, volumetry thresholds are provided but these are calculated directly from diameter thresholds. Additional time for volumetry is not reimbursed in the United States.

Table 1. Summary of key recommendations from Fleischner Society and British Thoracic Society guidelines for management of incidentally detected nodules

	Fleischner Society 2017	British Thoracic Society 2015
Scope	Incidentally detected nodules only	All nodules regardless of presentation route
Age	≥35 years	≥18 years
Solid nodules		
Volumetry or diameter preferred	Average diameter rounded to the nearest whole millimetre. (Volumetry threshold also provided)	Volumetry. Maximum diameter if volumetry not possible/ unreliable
Threshold for follow-up	6 mm	80 mm^3 or 5 mm
Initial management recommendation	Variable depending on nodule size and number: • 6–8 mm (100–250 mm^3) ◦ Single nodule- CT at 6–12 months ◦ Multiple nodules- CT at 3–6 months • > 8 mm (>250 mm^3) ◦ CT at 3 months/ PET CT or biopsy	Based on nodule size: • 80–300 mm^3 (5–8 mm) ◦ CT at 3 months • 5–6 mm (no volumetry available) CT at 12 months • >300 mm^3 (>8 mm) ◦ Risk assessment with Brock score ◦ ≥ 10% PET CT, followed by Herder score (<10% CT at 3 months; 10–70%—consider image-guided biopsy, excision or surveillance; >70% consider definitive treatment). ◦ < 10% CT at 3 months
Definition of growth	≥2 mm diameter	>25% increase in volume (volumetry or diameter measures where volumes not available) Clear visual evidence of growth
Duration of follow-up for stable nodules	Variable depending on nodule size and features: • 12–18 months if benign features and "unequivocally stable" • 18–24 months if high risk or multiple	Volumetry: • 12 months Diameter: • 24 months Can also consider discharge if VDT > 600 days
Subsolid nodules		
Volumetry or diameter preferred	Average diameter for entire nodule; maximum diameter for the solid component	Diameter
Threshold for follow-up	Depends on nodule number: • Single nodule—6 mm • Multiple nodules—no lower size threshold	5 mm
Initial management recommendation	Variable depending on nodule size, number and GGN or PSN • Multiple nodules/ <6 mm but high risk population (*e.g.* Asian): ◦ CT at 3–6 months • ≥6 mm ◦ Single GGN—CT at 6–12 months ◦ Single PSN—CT at 3–6 months ◦ Multiple (GGN & PSN)—CT at 3–6 months	CT scan at 3 months
Management recommendation/ surveillance interval for persisting nodules	• < 6 mm ◦ CT at 2 and 4 years (GGN & PSN) • ≥ 6 mm (≥100mm3) ◦ Single GGN—CT every 2 years ◦ Single PSN—CT every 1 year ◦ Multiple (GGN & PSN)—depends on most suspicious nodule	• Risk assessment with Brock score ◦ Low risk (<10%)—CT at 1 year, 2 years and 4 years ◦ High risk (> 10%) or concerning morphology (solid component presence or growth, pleural indentation, vacuolation)—consider image-guided biopsy, excision, non-surgical treatment or surveillance
Duration of follow-up for stable nodules	• Single nodule—5 years • Multiple nodules— guided by largest nodule	• 4 years

GGN, ground-glass nodules;PET, Positron emission tomography; PSN, part-solid nodule;VDT, volume doubling time.

NEW (INCIDENT) NODULES—WHAT TO DO

Current data suggest that between 3 and 13% of participants develop a new nodule annually after baseline screening.[10–14] Furthermore, new nodules are also encountered during follow up of incidentally detected nodules. Most of these nodules are solid, with new SSNs having an annual incidence of 1.5% in

IELCAP and in 0.9% over three screening rounds in the Dutch-Belgian screening trial (NELSON).[15,16] New SSN are likely to be inflammatory, with 67% in the NELSON study showing some resolution on interval scanning.[16] For these, initially a short interval (3 month) CT scan should be performed.

The NELSON group reviewed the data from their second (annual screening) or third (biannual screening) screening rounds. They defined new nodules as those either absent or smaller than 15 mm^3 on previous scans and assessed their likelihood of malignancy.[10] Overall, 4% of new nodules were malignant in their population, higher than for nodules detected at baseline. Furthermore, they found that the threshold for nodules having a higher rate of malignancy than in those participants without nodules was lower than for baseline nodules. This was 27 mm^3. Nodules between 27 mm^3 and 206 mm^3, and greater than 206 mm^3 had a malignancy rate of 3.1 and 16.9% respectively. This means that for new nodules, when a CT scan is available 1–2 years previously, a lower threshold for follow-up is appropriate. Reducing the threshold for further investigation from 300 mm^3 (recommended for baseline nodules) to 200 mm^3 might also be appropriate. A lower threshold may have implications for LDCT reading, because the detection and recording of very small nodules is more challenging and may take longer.

It is unclear whether these data would also be true for new nodules when the time interval between scans is less than 1 year (where rapid growth may indicate an inflammatory process) or more than 2 years (where lesion may represent indolent cancers or benign lesions). Table 2 summarises the different recommendations between the four main nodule guidelines for management of new solid nodules in the screening setting. Further research to assess the applicability in the non-screening setting is needed.

RISK PREDICTION MODELS—HOW AND WHEN TO USE THEM

All guidelines use clinical features of patients and morphological features of nodules to predict risk and guide management. BTS guidelines differ from the others in that they advocate the use of validated multivariable risk prediction models for larger solid nodules (>8 mm or >300 mm^3) or persisting SSNs. The Brock/ PanCan model is used at baseline, to stratify patients to either interval CT (risk < 10%) or positron emission tomography CT (PET-CT). After PET-CT, the Herder model is used and further management based on the probability of malignancy (Table 1).[2,17,18] Parameters for each model are summarised in Table 3.

Table 3. Brock and Herder Model variables

	Brock Model	Herder Model
Patient characteristics	Age	Age
	Gender	Smoking status
	Family history of lung cancer	Personal history of extrathoracic cancer
	Emphysema	
Nodule characteristics	Nodule size (diameter in mm)	Nodule size (diameter in mm)
	Nodule count	Nodule in upper lobe
	Nodule type	Spiculation
	Nodule in upper lobe	Nodule in upper lobe PET-CT avidity findings
	Spiculation	Spiculation

PET, Positron emission tomography.

Where multiple nodules are present, the recommendation would be to use the largest (or most suspicious) nodule to perform risk assessment on a baseline scan. The Brock score also incorporates nodule count as part of the risk prediction.[18] A key point is that these models should only be used on baseline scans, but not at subsequent timeframes- assessment of growth using volume doubling time should be employed to risk stratify and guide surveillance or more invasive testing/ treatment then.

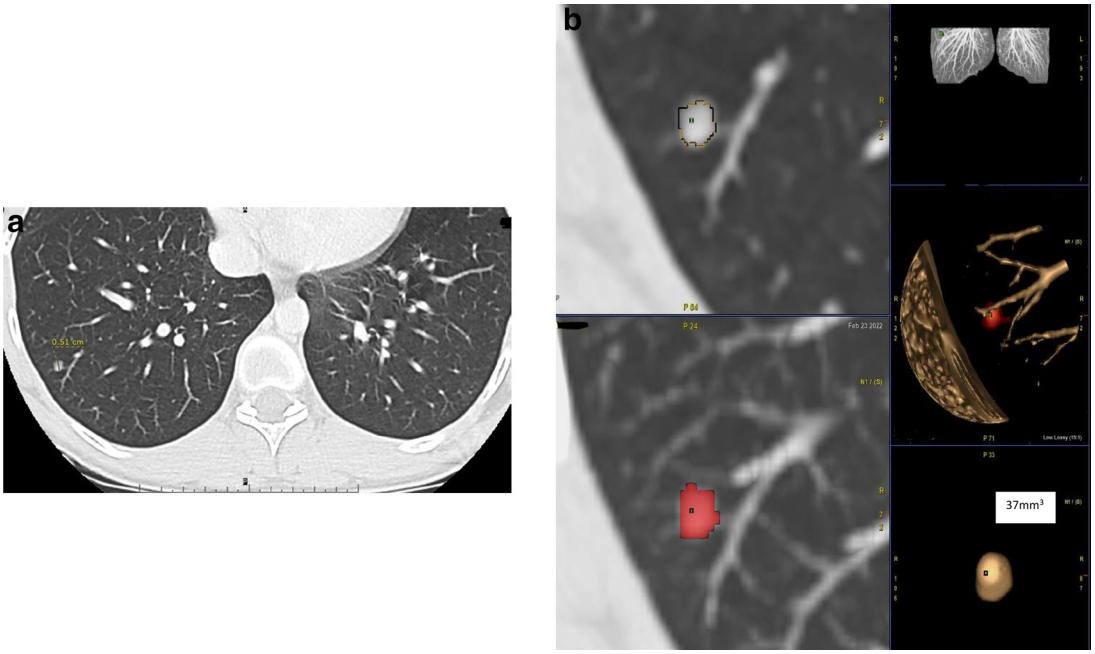
Although these models rely on manual measurement of diameter and clinician assessment of spiculation[19,20] they appear to

Table 2. Comparison of the key nodule guidelines regarding incident solid nodules and suggested management in screening

THRESHOLDS FOR ACTION ACCORDING TO CURRENT GUIDELINES				
ACTION	**BTS**	**Lung RADS * v. 1.1/NCCN**	**European Position Statement (Volumetry preferred)**	**I-ELCAP**
Annual screen	N/A	<4 mm <34 mm^3	<4 mm <30 mm^3	<3 mm
Extra CT	N/A	4 to 10 mm (PET-CT option if > 8 mm) (≥ 268 mm^3)	4–8 mm ≥100 to <200 mm^3	>3 mm (>3 mm to 5.9 mm, 6 month CT >6 mm to 14.9 mm, 1 month CT)
Work-up suggested	N/A	≥10 mm (≥524 mm^3) (PET-CT option if > 8 mm) (≥268 mm^3)	≥ 8 mm ≥200 mm^3	>15 mm

BTS, British Thoracic Society; I-ELCAP, International Early Lung Cancer Action Program; N/A, not applicable; NCCN, National Comprehensive Cancer Network; PET, Positron emission tomography.

Figure 1. (a) CT scan showing nodule measuring 5 mm maximum diameter. (b) Volumetry applied to the nodule in CT image. Figure 1a showing a volume of 37 mm^3.



work well in clinical practice. In an analysis of the combined lung cancer screening pilots in the UK, which employed BTS nodule guidelines, only 4.6% of surgical resections were for benign disease and there were no recorded harms in people without cancer.[21] The Brock and Herder models discriminate well in English populations but may not apply in some populations, *e.g.* those with a high background prevalence of fungal or granulomatous disease or low consumption of tobacco.[17,22–24]

VOLUME *VS* DIAMETER

BTS guidelines and the European statement favour using volumetry over diameter measurements in the assessment of nodules. Volumetry is preferred as it is more accurate and there is less variation in both absolute value and change in value (thus being a better measure of growth).[25] The error associated with manual measurements is around 1.5 mm, which may equate to a substantial change in volume for smaller nodules.[26] One paper suggested that, if a nodule were to change from 5 to 6 mm over 3 months (below the cut-off for growth on the basis of diameter), the volume doubling time would be 115 days. This growth rate is consistent with a potentially lethal malignancy.[25]

A further advantage of using volumetry over diameter is that it may allow more smaller nodules, above threshold for follow-up by calliper measurements, to be discharged at baseline due to the increased accuracy of volumetry. Figure 1a and b show an example of this. Volumetry also allows discharge at 12 months for stable solid nodules, whereas diameter measurements necessitate 24 months surveillance. This means that using volumetry, a considerable number of additional follow-up CT scans would be saved, something that is much needed in the National Health Service (NHS), where current and forecasted demand for radiology services exceeds capacity.

Central to establishing nodule volume is the requirement for accurate nodule segmentation.

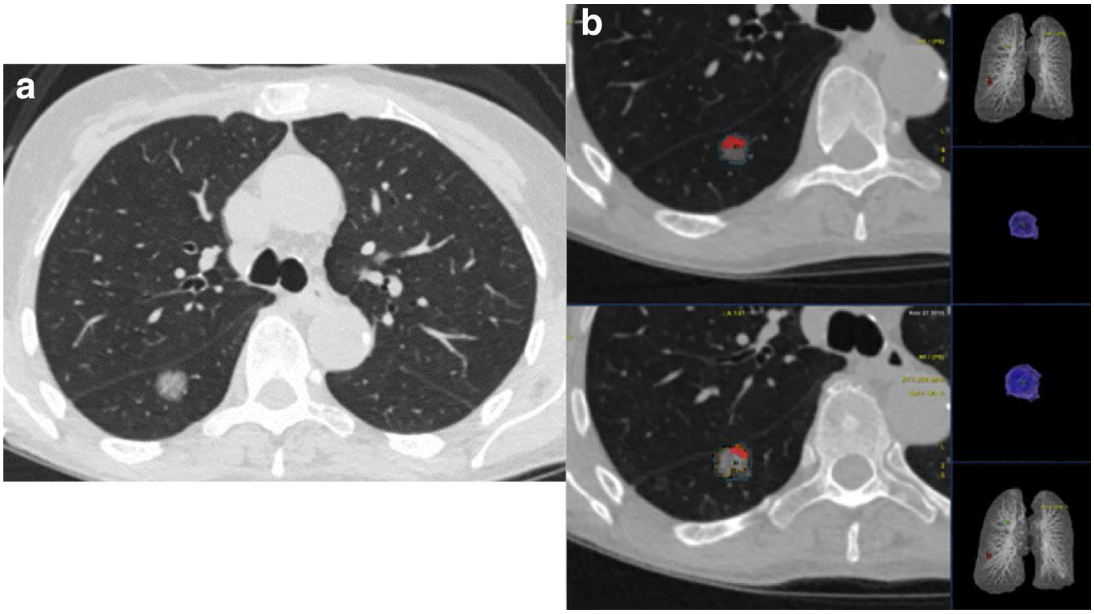
Volumetry may be less reliable for nodules in subpleural and juxtavascular locations as they can be more difficult to segment accurately.[27,28] Previous studies have shown interscan variability of ± 25% when patients with lung metastases were rescanned under identical conditions during the same session.[29,30] Bartlett et al have used more up to date CT scanners and modern volumetric software and have shown that this variability is less (±15%).[31] Where possible, it is important to use the same acquisition parameters and keep other scanning conditions as consistent as possible. Furthermore, different volumetry software packages should not be used interchangeably to assess serial scans in the same individual.

Volumetry for SSNs is more challenging than for solid lesions. (Figure 2) The main reason is the reduced difference in attenuation between the ground-glass component of a SSN and the surrounding lung parenchyma. A new metric combining nodule volume and density (termed nodule mass) may more promising as indicator of growth, but this may not reflect lethality and is still the focus of research.[32] For this reason, the BTS recommends the use of diameter to assess SSNs.

ARTIFICIAL INTELLIGENCE AND COMPUTER AIDED DETECTION

There is great interest in using machine learning techniques to detect and risk stratify pulmonary nodules. Artificial intelligence (AI)-based nodule prediction solutions have been shown to outperform existing multivariable models.[33,34] An AI model can account for nodule size, shape, location and other radiological factors consistently, without requiring subjective judgement or

Figure 2. (a) CT scan showing pure ground-glass nodule. (b) Volumetry applied to the nodule in CT image (Figure 2a).



data entry on the part of the clinician. Inter-reader variability in reporting morphology and nodule type is common, even amongst experienced thoracic radiologists.[35] In a study in the United States, a two-fold difference in recommendations was observed for the same group of patients following evaluation by different physicians.[36]

Several AI/CAD-based models have been developed and validated in recent years. A research team at Google produced a deep learning model which performed as well as radiologists in predicting malignancy in pulmonary nodules.[37] Optellum Ltd have developed and externally validated an AI-based CAD tool for lung cancer prediction in pulmonary nodules.[33,34] This was shown to outperform the Brock model in terms of discrimination, and allowed a larger proportion of benign nodules to be identified without missing cancers.[33] This has the potential to reduce radiology workload by avoiding unnecessary follow-up in benign nodules and enabling earlier identification of malignant nodules. It is currently the focus of a multicentre NHS implementation trial termed "DOLCE" (Determining the impact of Optellum's LCP artificial intelligence solution on service utilisation, health Economics and patient outcomes).[38]

Furthermore, the ability to systematically train and refine the model on many thousands of different images with a known outcome confers AI models with an edge in terms of diagnostic accuracy over non-AI models.[39] Although these AI solutions will help, a number of challenges remain, including patient selection bias, accountability and data privacy issues.[40,41] A platform to allow comparison and validation of AI tools is needed to fully define their role, clinical benefits and cost effectiveness.

SUBSOLID NODULES

Persistent part-solid nodules (PSNs), although less prevalent than solid nodules, are 1.4–5 times more likely to be malignant than solid nodules, but they often demonstrate very slow growth.[38,39]

Several large studies looking at the natural history of SSNs have been published since the BTS Guideline recommendations were made. One group followed up over 1200 PSNs and pure ground-glass nodules (pGGNs or non-solid) and showed that invasive adenocarcinoma was only seen in pGGN that developed a solid component. The median time to progression was 3.8 years.[42] The I-ELCAP group showed that the median transition time from non-solid to PSN in pGGNs was 25 months and there was 100% lung cancer specific survival in this group.[43] Longer term follow-up data from the National Lung Screening Trial suggest that even PSN have very good outcomes.[44] Data from the Multicenter Italian Lung Detection screening trial also showed a median time to lung cancer diagnosis of 52 months for SSN, with no lung cancer deaths attributed to SSN.[45] In light of this evidence, a more conservative approach, particularly for pGGNs may be appropriate as they are usually slowly growing and may not influence prognosis. However, in patients who are younger, it may be appropriate to offer a longer period of surveillance (beyond the 4 years suggested by the current BTS Guideline).

THE PULMONARY NODULE SERVICE

Many NHS hospital Trusts have dedicated pulmonary nodule multidisciplinary team (MDT) meetings to review incidentally detected nodules and advise on surveillance intervals. There is evidence that this improves adherence to guidelines.[46] The nodule MDT may include a respiratory physician, radiologist, radiographer, co-ordinator and nurse. Many of these are run as a "virtual" MDT. Patients who have low risk nodules, which can be discharged or simply require surveillance imaging, are contacted by letter informing them of the outcome. Only those at higher risk of malignancy and who require additional investigation would be seen in clinic. It is not necessary to "register" all pulmonary nodules at a nodule MDT in the same way as all lung cancer cases should be. The role of allied health professionals such as reporting radiographers can be of great help in

streamlining the MDT process and reducing the time taken to report nodule scans.[47,48]

SUMMARY AND CONCLUSIONS

Pulmonary nodules are a common incidental finding on CT scans of the chest both in the screening and non-screening setting. The lung cancer rate in these nodules has been shown to be more than 1.5% on a baseline scan (and may be higher for incident nodules). Importantly, when malignancy is detected these represent early-stage lung cancer which confers a good prognosis. Guidelines are essential, and need updating as evidence accumulates, to maximise benefits and minimise harms. An update to the BTS guidelines is currently underway, with publication expected in 2024.

CONFLICTS OF INTEREST

DRB reports honoraria from Astra Zeneca, MSD, MBS and Roche. EOD has no conflicts to disclose.

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