REVIEW ARTICLE

Management of pulmonary nodules

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ABSTRACT

Pulmonary nodules are frequently detected during clinical practice and require a structured approach in their management in order to identify early lung cancers and avoid harm from over investigation. The article reviews the 2015 British Thoracic Society guidelines for the management of pulmonary nodules and the evidence behind them.

Pulmonary nodules are frequently detected as incidental findings on CT performed for other reasons. With the increasing use of CT for both clinical indications and lung cancer screening, the number of pulmonary nodules detected is likely to grow significantly. Since pulmonary nodules may represent early lung cancers, a risk stratified approach to identify potential lung cancers at an early stage whilst avoiding harm and expense from over investigation of low risk nodules is important. The British Thoracic Society (BTS) published detailed and comprehensive guidance in 2015 following SIGN methodology and the Fleischner Society published updated guidance in 2017.[1]

DEFINITION OF A PULMONARY NODULE

A pulmonary nodule is a focal rounded or irregular opacity, which may be well- or poorly defined, measuring less than 30 mm in diameter and surrounded by aerated lung.[2] The definition used by guidelines has also included nodules in contact with the pleura but excludes those associated with lymphadenopathy or pleural disease.[3] Nodules are further categorised by their appearance into solid nodules and sub solid nodules since this has implications for the risk of malignancy and further management. Subsolid nodules (SSN) may either be a part-solid nodule (PSN), comprising of both solid and ground glass components (Figure 1), or a pure ground glass nodule (pGGN), the latter may also be referred to as "non-solid" (Figure 2). Ground glass refers to opacification that is greater than the background parenchyma but does not obscure the underlying bronchovascular structures.[2]

FREQUENCY OF PULMONARY NODULES

The frequency at which pulmonary nodules are detected depends on the indication for the imaging, threshold for reporting nodules, patient factors and geographical variations. Studies reporting the incidental finding of nodules on chest CT performed for other reasons, report a prevalence varying between 2 and 24% with a mean of 13%.[3] Lung cancer screening programmes have predominately recruited asymptomatic patients above 50 years of age with a significant smoking history. In this context nodule prevalence at baseline scan varied from 17 to 53% with a mean prevalence of 33%.[3] However the largest screening trials vary in the threshold for reporting detected nodules at baseline scans. In the US-based National Lung Screening Trial a prevalence of 26.8% of non-calcified nodules ≥4 mm was reported.[4] The Dutch NELSON trial reported all nodules ≥15mm3 with a prevalence of 50.5%, although only nodules ≥50 mm3 were considered significant at baseline screening.[5] The prevalence of pulmonary nodules may vary by region or country due the prevalence of granulomatous diseases.

CAUSES OF PULMONARY NODULES

The differential diagnosis of a pulmonary nodule is wide. Whilst malignancy is the primary concern, the majority of nodules are benign. Data from lung cancer screening trials suggest the prevalence of malignant nodules is 1.5%. This is similar to the prevalence of malignant nodules (1.4%) from studies examining nodules detected as an incidental finding.[3] Since the majority of nodules are small and do not exhibit growth, biopsy or excision should only follow careful assessment. Older case series of larger nodules prior to the introduction of more rigorous pre-operative risk stratification reported benign resection rates of 9–64% but application of the BTS guidelines has reduced this to below 5%.[6] The most common histological findings following resection of a benign lesion were granulomas, chondromas/hamartomas, intrapulmonary lymph nodes,

Figure 1. Part solid nodule in right upper lobe.
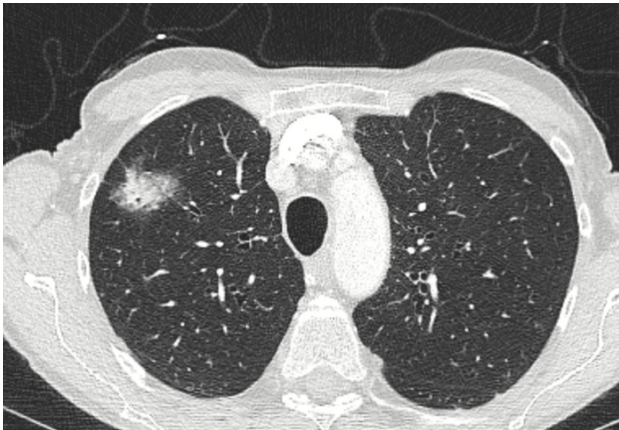
fibrosis and inflammatory lesions including pneumonia, abscess and aspergillomas.[7–12]

Patients with known malignancies will frequently undergo staging investigations or follow-up imaging following treatment to detect recurrence or metastases. The question over whether they represent benign lesions, metastatic disease or a new lung primary represents a difficult clinical problem. Hanamiya et al reported on 308 patients with solid malignancies of whom 75% had one or more lung nodules. 59% of these nodules were classified as benign after radiological follow up. Patients presenting with melanoma and sarcoma were more likely to have metastases than those with other primary malignancies in whom the majority of nodules were benign.[13] Kokhar et al reported the frequency of malignant nodules as 42% in a series of 151 patients with a non-lung solid malignancy and lung nodules. A new diagnosis of lung cancer was the most frequent cause of a malignant nodule in 21% of patients followed by metastases in 19% of patients.[14] Other studies reporting the prevalence of malignancy in biopsied or resected nodules only have reported higher rates of malignancy but conflicting results over whether co-existing lung cancer primaries[15,16] or metastatic disease[17] are more common. Larger nodule size, distance from the pleural margin, multiple

Figure 2. Pure ground glass nodule in right lower lobe.
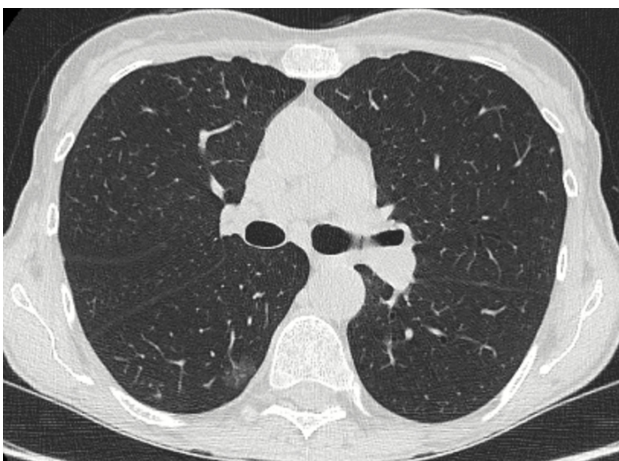
nodules and smoking have all been reported as factors associated with a higher probability of malignancy.[13,14,16]

The probability of malignancy in small pulmonary nodules detected in patients with otherwise resectable lung cancer has also been examined. Nodules were reported in 16–44% of scans with the majority of these nodules (60–95%) being classified as benign after radiological follow up.[18–20] Malignancy was more likely in patients with nodules in the same lobe as the primary, higher stage lung cancers[18] or where nodules were >10 mm in diameter.[19] BTS guidance suggests that co-existent nodules detected at the same time as an otherwise radically treatable lung cancer should not be assumed to be malignant and should be investigated in their own right.[3]

## INITIAL MANAGEMENT OF PULMONARY NODULES
Appropriate risk stratification is fundamental to management of pulmonary nodules to ensure that those with a high risk of malignancy are investigated and managed in a timely way, whilst avoiding over investigation and the reducing the potential for harm in lower risk patients. The BTS guidance suggests that nodules detected incidentally, through lung cancer screening or on staging investigations for cancer should all be assessed in the same way. Following the detection of a pulmonary nodule, both radiological and patient factors may be taken into account to determine the next most appropriate step.

CT FACTORS ASSOCIATED WITH BENIGN DISEASE
It is possible to safely reassure some patients at the baseline scan that the risk of a malignancy is extremely low and further follow up is not warranted. Traditionally, radiological stability over 2 years has been said to indicate a benign aetiology. This has been enshrined in previous guidelines[1] and was based upon studies in the 1950s from chest radiographs.[21] However it is recognised that some tumours may be extremely slow growing and it is not possible to define a safe period of stability at which tumours can be assumed to be benign.[22]

The BTS guideline recommends that nodules with a volume less than 80 mm^3 or a diameter <5 mm do not require further follow up (Figure 3). Data to support this approach come from the NELSON trial where the risk of malignancy in nodules <100 mm^3 or <5 mm in diameter was not significantly greater than the 0.4% risk of malignancy in screened subjects with no nodules.[23] Therefore, these small nodules do not confer any excess risk of malignancy. The BTS chose a lower volume threshold than the NELSON study since there may be a significant variability in volume measurements between software packages.[24,25]

Calcification within nodules in a diffuse, central or laminated pattern is typically seen with prior infections such as tuberculosis or histoplasmosis. Popcorn-like calcification is characteristic of chondroid calcification within a hamartoma.[26] The presence of these patterns of calcification is a reliable indicator of benign disease that does not warrant further follow up.

Figure 3. Algorithm for management of solid non-calcified nodules reproduced with permission from reference [3]
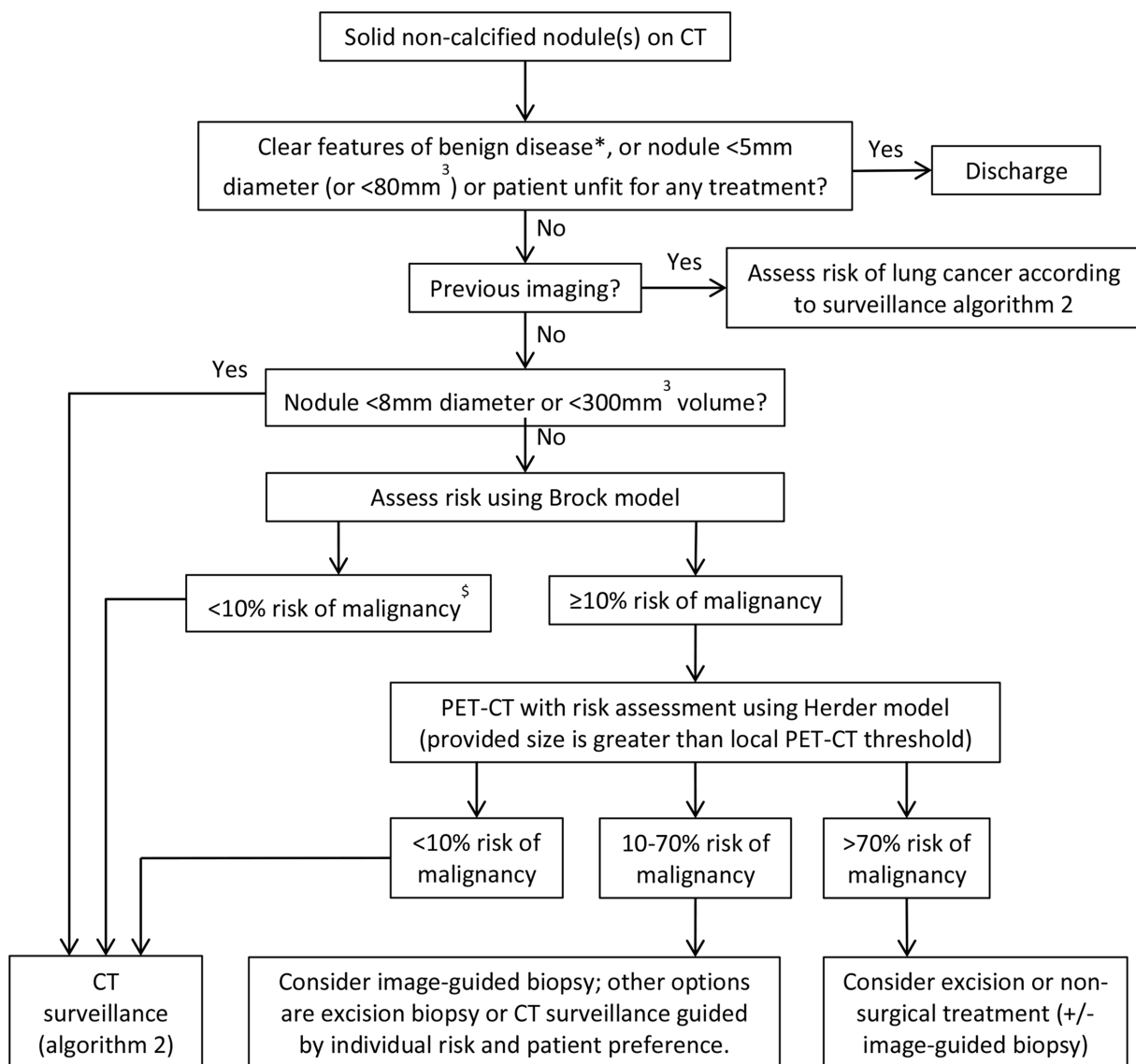
*e.g. hamartoma, typical peri-fissural nodule

$ Consider PET-CT for larger nodules in young patients with low risk by Brock score as this score was developed in screening cohort (50-75 years) so performance in younger patients unproven.

Solid nodules that appear as triangular or lentiform shapes, attached to fissures or adjacent to the pleura are classified as peri-fissural nodules (PFN) (Figure 4). The NELSON trial found that 19.7% of all nodules could be classified in this way. The majority of these nodules were small and remained stable in subsequent follow up, although 8.3% grew with a volume doubling time (VDT) of <400 days. However, none proved to be cancer after 5 years of follow up.[27] Studies examining the histological correlates of these lesions confirmed that those with the typical radiological findings were confirmed intrapulmonary lymph nodes on sampling.[28–31] Caution is needed when PFNs are larger than 10 mm or they display atypical features and consideration should be given to radiological follow up in these cases.

Further factors such as a smooth border or the presence of satellite nodules or cavitation have been associated with a benign aetiology, but the presence of the factors alone is not sufficient to exclude a malignancy.

CT AND PATIENT FACTORS ASSOCIATED WITH RISK OF MALIGNANCY

There are no features of nodules that are completely specific for malignancy. Identifying clinical and radiological factors associated with malignancy will help assess the risk of malignancy in an individual nodule and guide further management. There are number of radiological predictors of malignancy summarised in the BTS guideline following a review of the literature. These

Figure 4. Perifissural nodule adjacent to right oblique fissure.
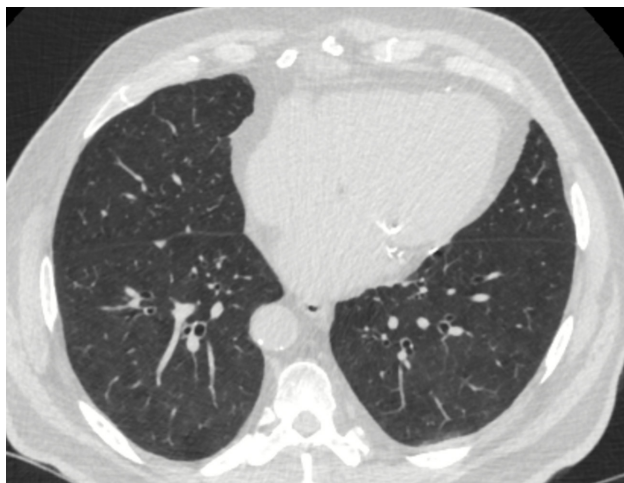
were: diameter, distance from pleura >10 mm, spiculation, ground-glass appearance, pleural indentation, vascular convergence, circumference diameter ratio, upper lobe location, volume, growth, air bronchogram, lymphadenopathy and cavity wall thickness. Of these predictors, nodule diameter, spiculation, upper lobe location, pleural indentation and a volume doubling time of <400 days were found consistently in two or more studies.

Patient factors also affect the probability that a pulmonary nodule is malignant. These include older age, current or ever smokers, time since quitting smoking, pack-years, family history of lung cancer, history of cancer >5 years before nodule detection, any history of previous cancer and haemoptysis. The current Fleischner guidance makes management recommendations on the basis low- or high-risk clinical and radiological features. Whilst the guidelines are not prescriptive on what constitutes a high-risk nodule, they suggest that patient age and smoking history are taken into account.[1] The BTS guidelines advocate the use of specific risk prediction models to calculate the probability of malignancy.

RISK PREDICTION MODELS

Whilst knowledge of both individual patient and radiological risk factors for malignancy is useful, clinicians have been shown to be less accurate at estimating the risk of malignancy than modern risk prediction models.[32,33] The BTS guideline recommends the use of the Brock model which has shown superior overall accuracy in several external validations, especially for nodules <10 mm where it is most often used in practice.[34–36] However, the Brock model may perform less well when assessing nodules in the context of recently active cancer, although the area under the curve of 0.82 is still as good as most other models.[37]

The BTS guideline recommends ongoing CT surveillance for nodules smaller than 8 mm or 300 mm^3 and for those larger nodules that have a Brock risk of <10%. Those patients with a probability of malignancy >10% should be referred for positron emission tomography (PET)-CT imaging to further refine the probability and guide further management.

CT SURVEILLANCE

The purpose of CT surveillance is to detect growth which is a strong predictor of malignancy and aggressiveness of the tumour.[38] Accurate growth assessment is more difficult in smaller nodules and where diameter measurements are used. BTS guidance suggests that for nodules 5–6 mm in diameter, a 12 month interval is required before growth can be assessed if diameter measurements are made whereas such nodules may be assessed at 3 months where volumetry is used. Nodules ≥ 6 mm or ≥80 mm^3 are scanned at 3 months. Where there is no significant growth in a nodule at 3 months, a further interval scan at 1 year from the baseline scan is recommended (Figure 5). The BTS guideline recommends semi-automated volumetry as the preferred measurement method. Where volumetry is not possible then maximum axial diameter is used (also used in the Brock model). In contrast, The Fleischner Society, as well as providing some volumetry parameters, give a detailed description of a method to calculated average diameter from three orthogonal planes.[39]

When compared to two-dimensional measurements, automated volumetry is more accurate, particularly when nodule margins are irregular. The interobserver variability of manual diameter measurements exceed the threshold of 1.5 mm at which growth is considered significant.[1,40,41] Gietema et al[42] found that only 11% of volumetric measurements had a significant interobserver difference when performing measurements on the same scan. However, volumetry also shows significant variability in measurements with the 95% confidence interval of agreement of ±22.5%, with irregular nodule shape being associated with the variability. Therefore, a cut-off of at least 25% has been proposed as defining significant growth between scans and is recommended in the BTS guidelines. Assessment of growth rate by volumetry may allow a shorter interval to detect malignant growth rates, particularly in irregularly shaped nodules.[43,44]

Both the BTS and Fleischner society guidelines recommend the use of low-radiation dose CT, given the potential for repeated exposures during follow up. Techniques to reduce the radiation dose include adjusting exposure factors according to patient body habitus and the use of iterative reconstruction and dose modulation. Low-dose CT does not significantly reduce the sensitivity of nodule detection compared to standard-dose CT.[45–47] Nodule detection, characterisation and assessment of growth is aided by the use of thin-section CT.[48–50] The BTS guidelines recommend a slice thickness of no more than 1.25 mm. The use of multiplanar reconstruction, maximum intensity projection and volume rendering improves the sensitivity of nodule detection.[51–55] Given the variability in nodule detection and characterisation with differing scan parameters, similar techniques for follow up scans should be used to avoid interscan variability.[1]

GROWTH PATTERNS

A wide range of growth rates have been reported for lung cancers, with histological subtype strongly affecting VDT and adenocarcinoma showing the most variation, reflecting the know heterogeneity in this subtype.

Figure 5. Algorithm for CT surveillance of solid nodules reproduced with permission from reference [3]. VDT, volume doubling time.
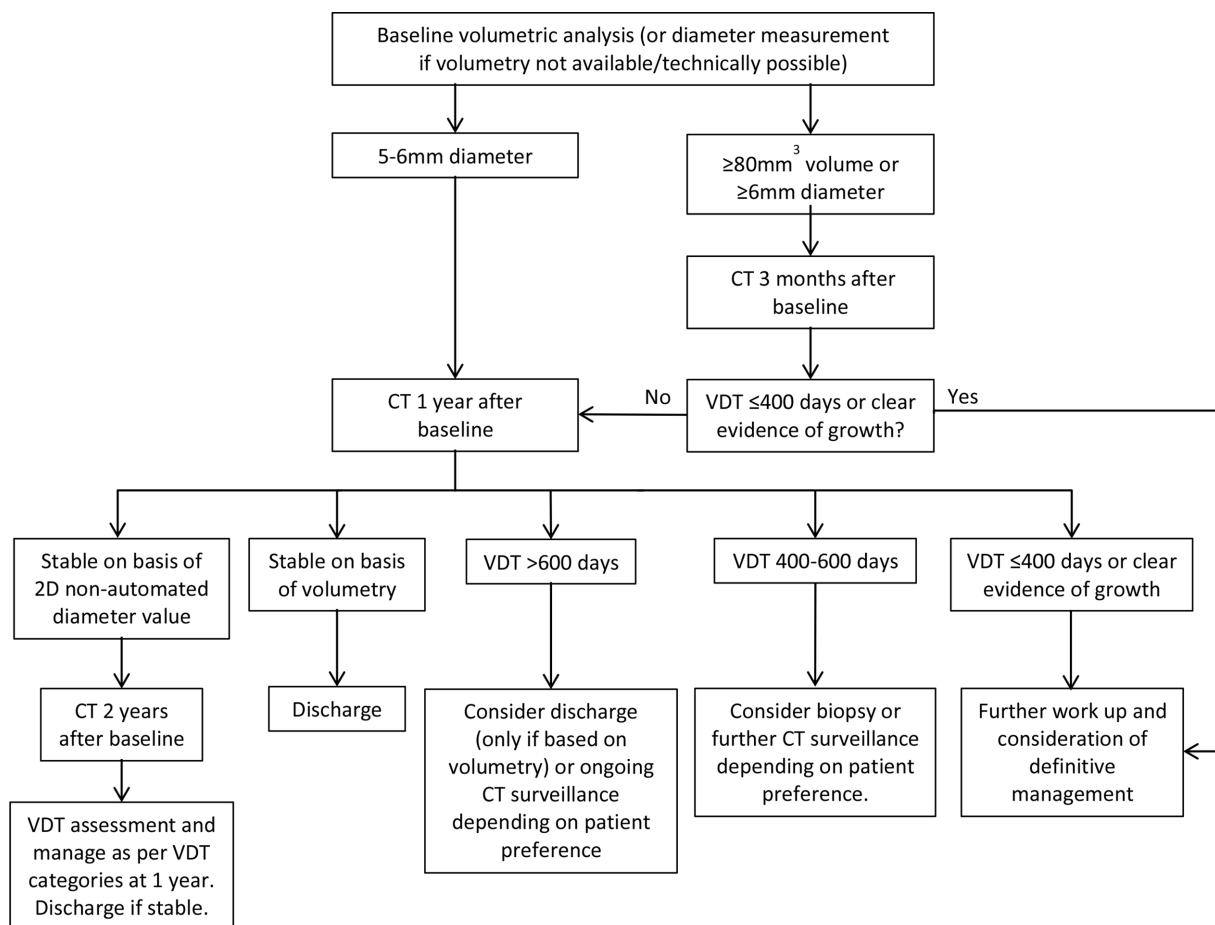
The NELSON study used a VDT of <400 days and >25% increase in volume to indicate the need for further investigation. In patients with a VDT of <400 days, the probability of malignancy was 9.9% compared to 4% in those patients with a VDT of 400–600 days. The probability of malignancy for a nodule with a VDT of >600 days was 0.8% and not significantly different from the 0.4% probability of malignancy in patients with no nodules.[56] Similarly, a further screening study found that all solid nodules which were subsequently proven to be malignant had a VDT < 400 days whilst only 3% of lung cancers had a VDT > 400 days and all were subsolid nodules.[57] Whilst there is a trend to an increase risk of malignancy with slow growing nodules, the risks of further investigation and treatment should be borne in mind and discussed with the patient.

Consequently, guidance recommends that patients with a nodule VDT < 400 days be referred on for further assessment and management of the nodule. Where the VDT is between 400 and 600 days, biopsy or further surveillance may be considered taking into account patient preferences, age and fitness. Discharge from surveillance or further follow up for nodules with a VDT > 600 days may be considered after counselling the patient. When using volumetry, a lack of significant change in nodule volume at 1 year allows for confident discharge from further surveillance. The optimal duration of follow up is not known when nodule diameter is used, and therefore a further scan at 2 years from baseline is recommended to ensure ongoing stability before discharge.

MANAGEMENT OF HIGHER RISK NODULES
BTS guidelines recommend PET-CT for nodules ≥ 8 mm in diameter or 300 mm^3 with a risk of malignancy >10% followed by further assessment with the Herder model.

The majority of lung cancers show ^{18}fluodeoxyglucose (FDG) uptake (Figure 6) but false positives and false negatives may occur. Infective and inflammatory nodules may demonstrate FDG uptake in conditions such as tuberculosis or sarcoidosis. Thus, PET-CT is less accurate in populations with a high prevalence of granulomatous disease.[58] False negatives may occur in mucinous tumours, lepidic pattern adenocarcinomas or well-differentiated adenocarcinomas.[59] Tumours close to the diaphragm may show significant motion artefact causing misregistration and underestimation of FDG uptake.

The Herder model was developed from the Mayo risk prediction tool but with the addition of PET findings to further refine the model. This was found to improve the area under the curve from 0.79 to 0.92. It has also been validated in a UK cohort and performed the best of all the risk prediction models for higher risk

Figure 6. Spiculate node left upper lobe nodule (a) with intense [18]FDF uptake on PET-CT (b). [18]FDG, 18-fludeoxyglucose; PET, positron emissiontomography.

A

B
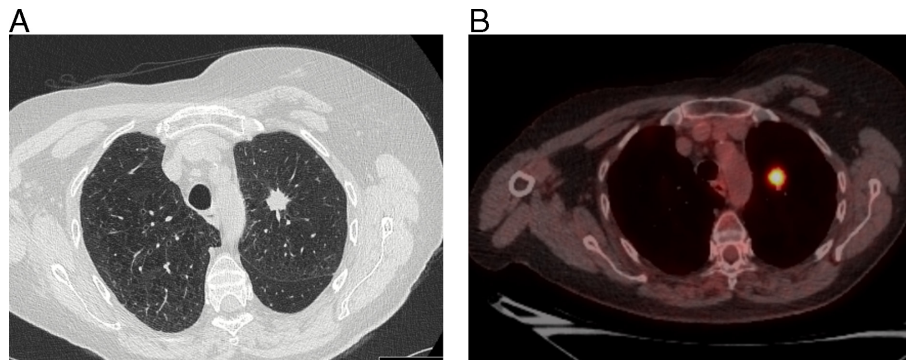
nodules.[34] In the model, Herder classified uptake in nodules on a 4-point scale (Table 1). Whilst they did not state what thresholds were used for each category, other authors have, using a comparison to the uptake in the mediastinal blood pool.[60,61] Therefore PET-CT scans should report uptake in nodules in a standardised way to allow findings to be incorporated into the Herder risk prediction tool and therefore follow clinical algorithms.

In the BTS guideline, a Herder score less than 10% risk of malignancy prompts further CT surveillance. For nodules with an intermediate risk of 10–70%, the options are of biopsy or continued surveillance following discussion with the patient. Nodules with a probability of malignancy >70%, image guide biopsy, excision or non-surgical treatment may be considered.

SUBSOLID NODULES
Subsolid nodules require a different management approach to solid nodules. They are more frequently multiple and may represent pre-invasive or invasive lesions. Whilst they are more likely to be malignant than solid nodules, the prognosis is often better, since they are more likely to represent slow-growing malignancies. In the PanCan and BCC screening trials 9.3–15.9% of all nodules were classified as pGGNs and 0.9–4.3% were classified as PSNs.[62] The ELCAP trial reported an overall prevalence of 2.8% for pGGNs and 1.6% for PSNs.[63] The histological correlates of these include atypical adenomatous hyperplasia, adenocarcinoma-in-site, minimally invasive adenocarcinoma and invasive adenocarcinoma.[64,65] Whilst the majority of SSNs are benign, the risk is increased in PSNs, particularly larger lesions and those with growth of more than 2 mm during follow up.[65] Age, previous history of lung cancer, smoking status, pleural indentation and a bubble-like

appearance are all associated with an increased risk of malignancy. A peripheral eosinophilia is associated with a reduced probability of malignancy.[66–68]

Up to a third of SSNs may resolve after a 3 month period of surveillance,[66] therefore the BTS guidelines recommend a repeat CT in the first instance (Figure 7). Approximately, one quarter of SSNs will grow over a period of up to 4 years, but a larger proportion of PSNs may demonstrate growth over a 5 year period. Nodule size, age and smoking history have all been associated with an increased risk of growth.[64,69,70] Growth of more than 2 mm in an SSN is considered significant, since the majority of nodules showing growth ≥2 mm were demonstrated to be malignant in one study.[64] Lymph node metastases are related to the size of the solid component in a lesion and the rate is <1% in pGGN or PSNs with a solid component <10 mm.[65,71] Whilst growing lesions have a high probability of malignancy, the volume doubling time is frequently very long suggesting a more indolent course. Therefore, there may be a risk of over diagnosis in these lesions and for some patients a more conservative approach may be appropriate.[72] In a study from the IELCAP group, pGGN of any size could be observed for at least 12 months without an adverse effect on prognosis.[73] Patient wishes, natural life expectancy and fitness for invasive investigations or treatment should all be taken into account when considering further investigation. Where pGGN have transition to PSN, the outcome from sub lobar resection of SSNs is good with low operative mortality and low risk of recurrence.[74–76]
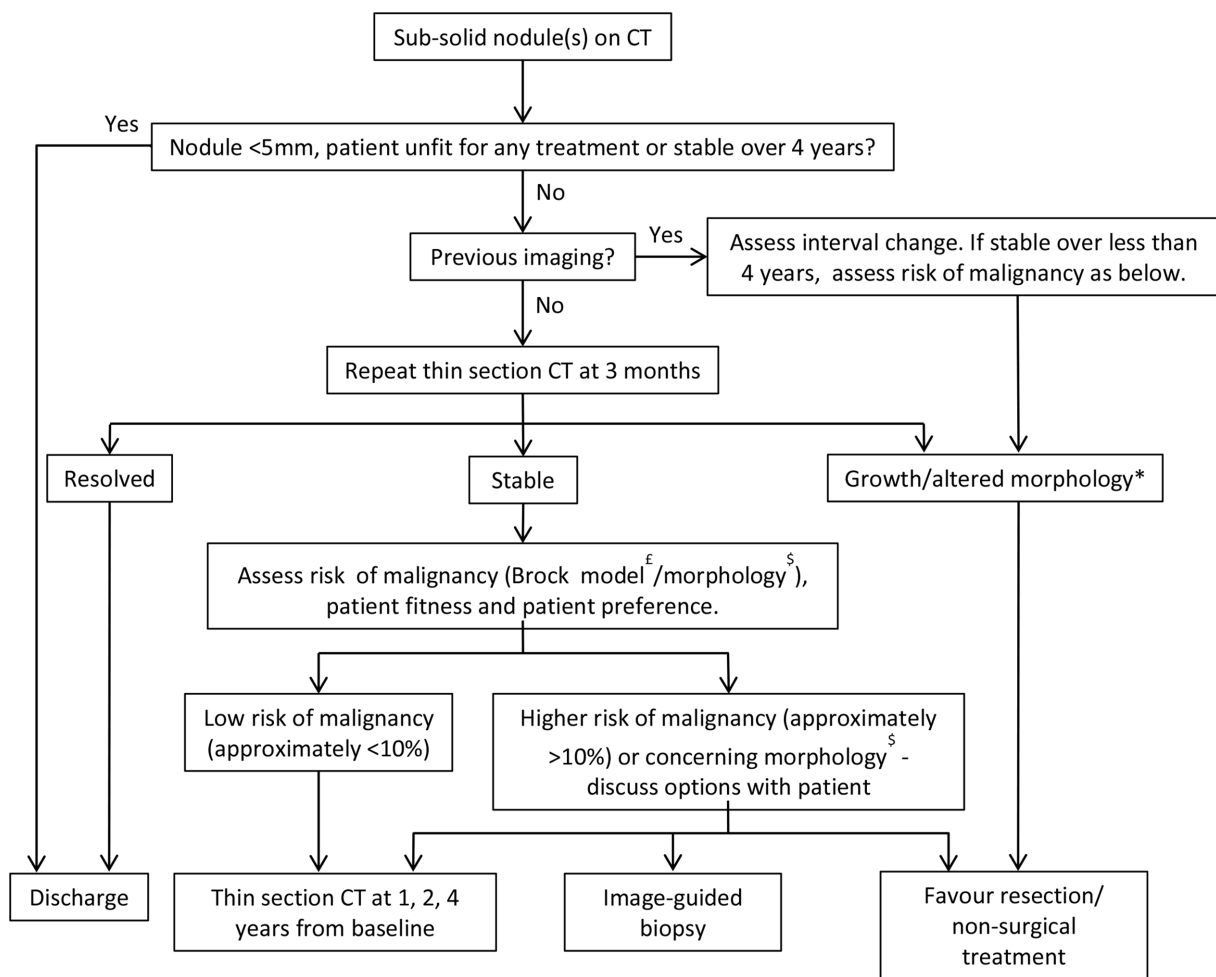
For stable SSNs, the BTS guidelines recommend risk assessment with the Brock risk score calculator, with the proviso that it may underestimate the probability of malignancy, since it was developed using baseline CT scans which included nodules that subsequently resolved. Nodules with a probability of malignancy <10% may undergo a longer surveillance period with repeat thin-section CT at 1, 2 and 4 years from baseline. Those with an intermediate probability of malignancy (10–70%) should be counselled about the choices between continued surveillance, image-guided biopsy and resection or non-surgical treatments (for PSN).

Table 1. Herder FDG intensity scale with BTS descriptions

Intensity	Description
Absent	Uptake indiscernible from background lung tissue
Faint	Uptake less than or equal to mediastinal blood pool
Moderate	Uptake greater than mediastinal blood pool
Intense	Uptake markedly greater than mediastinal blood pool

BTS, BritishThoracic Society; FDG, fludeoxyglucose.

Figure 7. Algorithm for the management of sub solid nodules reproduced with permission from reference 3.


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                        ┌─────────────────────────┐
                        │  Sub-solid nodule(s) on CT │
                        └─────────────────────────┘
                                    │
      Yes     ┌──────────────────────────────────────────────────────┐
      ◄───────│ Nodule <5mm, patient unfit for any treatment or stable over 4 years? │
              └──────────────────────────────────────────────────────┘
                                    │ No
                        ┌────────────────────┐   Yes   ┌────────────────────────────────────┐
                        │ Previous imaging?   │────────►│ Assess interval change. If stable over less than │
                        └────────────────────┘         │ 4 years,  assess risk of malignancy as below.    │
                                    │ No               └────────────────────────────────────┘
                        ┌────────────────────────────┐
                        │ Repeat thin section CT at 3 months │
                        └────────────────────────────┘
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* Change in mass/new solid component
£ Brock model may underestimate risk of malignancy in SSN that persist at 3
$ Size of the solid component in PSN, pleural indentation and bubble-like

BIOPSY TECHNIQUES

A number of techniques for obtaining tissue are available and choice will be guided by local expertise, the nature of the nodule and the potential risks to the patient.

CT guided biospy

CT-guided biopsy is the most widely used procedure for obtaining histological confirmation. The BTS guideline examined the literature and reported an overall sensitivity of 90.7% and a specificity of 93.9%. The average negative likelihood ratio was 0.1. The post-test probability of malignancy is heavily dependent on the pre-test probability and therefore knowledge of the negative likelihood ratio is extremely important in determining the next steps if a negative biopsy result is received. A patient with a pre-test probability of 90% will still have a post-test probability of 50% indicating that a malignancy cannot be excluded. However, a patient with a pre-test probability of 50% and a negative biopsy will only have a 10% post-test probability of malignancy. Therefore, consideration of a repeat biopsy should be

given to patients where there is ongoing doubt since the majority of repeat biopsies will yield a diagnosis.[77]

Accuracy of CT-guided biopsy declines with decreasing nodule size,[78–81] although high sensitivity and specificity is still reported in case series of nodules <10 mm undergoing biopsy.[82] A long needle tract may also reduce diagnostic accuracy or the ability to obtain adequate samples for analysis.[80,83] PSNs and pGGNs in particular have been shown to have a lower diagnostic accuracy than solid nodules.[82,84] The use of cone beam CT to provide real time fluoroscopic images and multiplanar reformatting have been associated with increased diagnostic accuracy.[85–88]

The most common complication of CT-guided biopsy is pneumothorax. In the largest case series reporting complications, 15% of patients developed a pneumothorax post-biopsy with 6% requiring intercostal drainage. Haemorrhage occurred in 1% of patients and air embolism in 0.5% with death occurring in one patient (0.16%).[89] Low FEV_1, presence of emphysema along the

needle tract, longer needle path, number of punctures, upper lobe location and core-needle biopsy are all associated with an increased risk.

Bronchoscopic biopsy

Conventional bronchoscopy has a low sensitivity in diagnosing pulmonary nodules, reported at 13.5% in a substudy of patients in the NELSON trial.[90] This may be significantly increased by the use of fluoroscopy but the yield varies depending on the location of the nodule, with yields higher for more proximal and larger nodules.[91–93]

Pulmonary nodules may be located by radial endobronchial ultrasound by directing a catheter containing a rotating ultrasound probe into the distal airways. Ultrasound images show characteristic changes when entering an airway surrounded by a solid lesion. The catheter is left in place and the lesion may be aspirated or a transbronchial biopsy taken by advancing forceps to the lesion. In a meta-analysis of 54 studies analysing the results of 7285 nodules, the diagnostic yield was 70.6%. A higher diagnostic yield was reported for malignant lesions (72.4%) and for lesions >2 cm and where there was the presence of the bronchus sign on CT (an airway entering the lesion). The authors did not report the pooled sensitivity and specificity. The overall rate of complications was 2.8% of which pneumothorax was most common followed by bleeding. Intercostal drain was required in 0.2%.[94]

Electromagnetic navigational bronchoscopy involves using a steerable probe directed through a bronchoscope whilst the patient lies on a board creating an electromagnetic field. A virtual bronchoscopic map of the airways is generated from a CT scan of the patient's chest and key points are registered to align the anatomy. A meta-analysis of 15 studies examining 1033 nodules reported an overall yield of 64.9%. There was a 71.1% sensitivity for malignancy and a negative predictive value of 52%. Pneumothorax occurred in 3% of patients. An increased yield was associated with nodules located in the middle or upper lobes, increased size, the presence of the bronchus sign, aspiration techniques over biopsy forceps and when a combined radial endobronchial ultrasound was used.[95]

Surgical biopsy

Surgical biopsy may be considered where there is a high clinical suspicion of malignancy despite a benign or indeterminate biopsy result or where a nodule is considered of sufficiently high risk that it warrants excision biopsy without attempt at biopsy first. The risks of surgical resection should be balanced against the possibility of stage progression during a period of radiological surveillance. The choice of excision biopsy will depend on a number of factors including patient preference, fitness for surgery and the location and size of the nodule. Small, deep or SSNs may be particularly hard for to find at video assisted thoracoscopic surgery, and therefore may require a thoracotomy and/or lobectomy for diagnosis. An on-table frozen section may be performed for diagnosis before proceeding to lobar resection and lymph node sampling for confirmed malignancies.

Direct to resection pathways have been associated with a faster route to diagnosis, lower hospital costs and shorter length of stay.[96,97] There is no agreed acceptable benign resection rate for undiagnosed pulmonary nodules but this is lowering.

CONCLUSIONS

Pulmonary nodules are increasingly detected as incidental findings on CT scans. The advent of lung cancer screening means that there will be an increasing workload for radiology departments and nodule multidisciplinary teams. Following evidence-based guidelines for pulmonary nodule management will ensure that lung cancers are detected and treated early whilst minimising the harm to patients and ensuring the best use of resources.

REFERENCES

1. MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. *Radiology* 2017; **284**: 228–43. doi: https://doi.org/10.1148/radiol.2017161659

2. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner society: glossary of terms for thoracic imaging. *Radiology* 2008; **246**: 697–722. doi: https://doi.org/10.1148/radiol.2462070712

3. Callister MEJ, Baldwin DR, Akram AR, Barnard S, Cane P, Draffan J, et al. British Thoracic Society guidelines for the investigation and management of pulmonary nodules. *Thorax* 2015; **70 Suppl 2**(Suppl 2): ii1–54. doi: https://doi.org/10.1136/thoraxjnl-2015-207168

4. Church TR, Black WC, Aberle DR, Berg CD, Clingan KL, Duan F, et al. Results of initial low-dose computed tomographic screening for lung cancer. *N Engl J Med* 2013; **368**: 1980–91. doi: https://doi.org/10.1056/NEJMoa1209120

5. van Klaveren RJ, Oudkerk M, Prokop M, Scholten ET, Nackaerts K, Vernhout R et al. Management of Lung Nodules Detected by Volume CT Scanning [Internet]. 2009. http://dx.doi.org/10.1056/NEJMoa0906085. 2009 [cited 2018 Nov 24]. Available from: https://www.nejm.org/doi/10.1056/NEJMoa0906085?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dwww.ncbi.nlm.nih.gov [cited 2018 Nov 24].

6. Crosbie PA, Balata H, Evison M, Atack M, Bayliss-Brideaux V, Colligan D, et al. Second round results from the Manchester 'Lung Health Check' community-based targeted lung cancer screening pilot. *Thorax* 2018: thoraxjnl-2018-212547. doi: https://doi.org/10.1136/thoraxjnl-2018-212547

7. Jiménez MF. Prospective study on video-assisted thoracoscopic surgery in the resection of pulmonary nodules: 209 cases from the Spanish video-assisted thoracic surgery Study Group. *European Journal of Cardio-Thoracic Surgery* 2001; **19**: 562–5. doi: https://doi.org/10.1016/S1010-7940(01)00650-9

8.   Walker BL, Williamson C, Regis SM, McKee AB, D'Agostino RS, Hesketh PJ, et al. Surgical outcomes in a large, clinical, low-dose computed tomographic lung cancer screening program. *Ann Thorac Surg* 2015; **100**: 1218–23. doi: https://doi.org/10.1016/j.athoracsur.2015.04.112

9.   Toomes H, Delphendahl A, Manke HG, Vogt-Moykopf I. The coin lesion of the lung. A review of 955 resected coin lesions. *Cancer* 1983; **51**: 534–7. doi: https://doi.org/10.1002/1097-0142(19830201)51:3<534::AID-CNCR2820510328>3.0.CO;2-B

10. Pericelli A, Imperatori A, Vassallo F, Rotolo N, Dominioni L. Resection of small indeterminate lung nodules by video-assisted thoracoscopic surgery (VTS). Implications for the early diagnosis of lung cancer. *Rays* 2004; **29**: 387–90.

11. Ludwig C, Zeitoun M, Stoelben E. Video-assisted thoracoscopic resection of pulmonary lesions. *Eur J Surg Oncol* 2004; **30**: 1118–22. doi: https://doi.org/10.1016/j.ejso.2004.07.005

12. Smith MA, Battafarano RJ, Meyers BF, Zoole JB, Cooper JD, Patterson GA. Prevalence of benign disease in patients undergoing resection for suspected lung cancer. *Ann Thorac Surg* 2006; **81**: 1824–9; discussion 1828-1829. doi: https://doi.org/10.1016/j.athoracsur.2005.11.010

13. Hanamiya M, Aoki T, Yamashita Y, Kawanami S, Korogi Y. Frequency and significance of pulmonary nodules on thin-section CT in patients with extrapulmonary malignant neoplasms. *Eur J Radiol* 2012; **81**: 152–7. doi: https://doi.org/10.1016/j.ejrad.2010.08.013

14. Khokhar S, Vickers A, Moore MS, Mironov S, Stover DE, Feinstein MB. Significance of non-calcified pulmonary nodules in patients with extrapulmonary cancers. *Thorax* 2006; **61**: 331–6. doi: https://doi.org/10.1136/thx.2005.051508

15. Quint LE, Park CH, Iannettoni MD. Solitary pulmonary nodules in patients with extrapulmonary neoplasms. *Radiology* 2000; **217**: 257–61. doi: https://doi.org/10.1148/radiology.217.1.r00oc20257

16. Mery CM, Pappas AN, Bueno R, Mentzer SJ, Lukanich JM, Sugarbaker DJ, et al. Relationship between a history of antecedent cancer and the probability of malignancy for a solitary pulmonary nodule. *Chest* 2004; **125**: 2175–81. doi: https://doi.org/10.1378/chest.125.6.2175

17. Caparica R, Mak MP, Rocha CH, Velho PHI, Viana P, Moura MRL, et al. Pulmonary nodules in patients with Nonpulmonary cancer: not always metastases. *J Glob Oncol* 2016; **2**: 138–44. doi: https://doi.org/10.1200/JGO.2015.002089

18. Yuan Y, Matsumoto T, Hiyama A, Miura G, Tanaka N, Emoto T, et al. The probability of malignancy in small pulmonary nodules coexisting with potentially operable lung cancer detected by CT. *Eur Radiol* 2003; **13**: 2447–53. doi: https://doi.org/10.1007/s00330-003-1905-9

19. Kim YH, Lee KS, Primack SL, Kim H, Kwon OJ, Kim TS, et al. Small pulmonary nodules on CT accompanying surgically resectable lung cancer: likelihood of malignancy. *J Thorac Imaging* 2002; **17**: 40–6. doi: https://doi.org/10.1097/00005382-200201000-00005

20. Keogan MT, Tung KT, Kaplan DK, Goldstraw PJ, Hansell DM. The significance of pulmonary nodules detected on CT staging for lung cancer. *Clin Radiol* 1993; **48**: 94–6. doi: https://doi.org/10.1016/S0009-9260(05)81079-7

21. Good CA, Wilson TW. The solitary circumscribed pulmonary nodule; study of seven hundred five cases encountered roentgenologically in a period of three and one-half years. *J Am Med Assoc* 1958; **166**: 210–5.

22. Yankelevitz DF, Henschke CI. Does 2-year stability imply that pulmonary nodules are benign? *American Journal of Roentgenology* 1997; **168**: 325–8. doi: https://doi.org/10.2214/ajr.168.2.9016198

23. Horeweg N, van Rosmalen J, Heuvelmans MA, van der Aalst CM, Vliegenthart R, Scholten ET, et al. Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the Nelson trial of low-dose CT screening. *Lancet Oncol* 2014; **15**: 1332–41. doi: https://doi.org/10.1016/S1470-2045(14)70389-4

24. de Hoop B, Gietema H, van Ginneken B, Zanen P, Groenewegen G, Prokop M. A comparison of six software packages for evaluation of solid lung nodules using semi-automated volumetry: what is the minimum increase in size to detect growth in repeated CT examinations. *Eur Radiol* 2009; **19**: 800–8. doi: https://doi.org/10.1007/s00330-008-1229-x

25. Zhao YR, van Ooijen PMA, Dorrius MD, Heuvelmans M, de Bock GH, Vliegenthart R, van OPM, de BGH, et al. Comparison of three software systems for semi-automatic volumetry of pulmonary nodules on baseline and follow-up CT examinations. *Acta Radiol* 2014; **55**: 691–8. doi: https://doi.org/10.1177/0284185113508177

26. Erasmus JJ, Connolly JE, McAdams HP, Roggli VL. Solitary pulmonary nodules: Part I. morphologic evaluation for differentiation of benign and malignant lesions. *Radiographics* 2000; **20**: 43–58. doi: https://doi.org/10.1148/radiographics.20.1.g00ja0343

27. de Hoop B, van Ginneken B, Gietema H, Prokop M. Pulmonary perifissural nodules on CT scans: rapid growth is not a predictor of malignancy. *Radiology* 2012; **265**: 611–6. doi: https://doi.org/10.1148/radiol.12112351

28. Wang C-W, Teng Y-H, Huang C-C, Wu Y-C, Chao Y-K, Wu C-T, Y-C W, C-T W. Intrapulmonary lymph nodes: computed tomography findings with histopathologic correlations. *Clin Imaging* 2013; **37**: 487–92. doi: https://doi.org/10.1016/j.clinimag.2012.09.010

29. Shaham D, Vazquez M, Bogot NR, Henschke CI, Yankelevitz DF. CT features of intrapulmonary lymph nodes confirmed by cytology. *Clin Imaging* 2010; **34**: 185–90. doi: https://doi.org/10.1016/j.clinimag.2009.05.005

30. Hyodo T, Kanazawa S, Dendo S, Kobayashi K, Hayashi H, Kouno Y, et al. Intrapulmonary lymph nodes: thin-section CT findings, pathological findings, and CT differential diagnosis from pulmonary metastatic nodules. *Acta Med Okayama* 2004; **58**: 235–40. doi: https://doi.org/10.18926/AMO/32102

31. Oshiro Y, Kusumoto M, Moriyama N, Kaneko M, Suzuki K, Asamura H, et al. Intrapulmonary lymph nodes: thin-section CT features of 19 nodules. *J Comput Assist Tomogr* 2002; **26**: 553–7. doi: https://doi.org/10.1097/00004728-200207000-00014

32. Swensen SJ, Silverstein MD, Edell ES, Trastek VF, Aughenbaugh GL, Ilstrup DM, et al. Solitary pulmonary nodules: clinical prediction model versus physicians. *Mayo Clin Proc* 1999; **74**: 319–29. doi: https://doi.org/10.4065/74.4.319

33. Gurney JW, Lyddon DM, McKay JA. Determining the likelihood of malignancy in solitary pulmonary nodules with Bayesian analysis. Part II. Application. *Radiology* 1993; **186**: 415–22. doi: https://doi.org/10.1148/radiology.186.2.8421744

34. Al-Ameri A, Malhotra P, Thygesen H, Plant PK, Vaidyanathan S, Karthik S, et al. Risk of malignancy in pulmonary nodules: a validation study of four prediction models. *Lung Cancer* 2015; **89**: 27–30. doi: https://doi.org/10.1016/j.lungcan.2015.03.018

35. Winkler Wille MM, van Riel SJ, Saghir Z, Dirksen A, Pedersen JH, Jacobs C, et al. Predictive accuracy of the PanCan lung cancer risk prediction model -external validation based on CT from the Danish lung cancer screening trial. *Eur Radiol* 2015; **25**: 3093–9. doi: https://doi.org/10.1007/s00330-015-3689-0

36. van Riel SJ, Ciompi F, Jacobs C, Winkler Wille MM, Scholten ET, Naqibullah M, et al. Malignancy risk estimation of screen-detected nodules at baseline CT: comparison of the PanCan model, Lung-RADS and NCCN guidelines. *Eur Radiol* 2017; **27**: 4019–29. doi: https://doi.org/10.1007/s00330-017-4767-2

37. Talwar A, Rahman NM, Kadir T, Pickup LC, Gleeson F. A retrospective validation study of three models to estimate the probability of malignancy in patients with small pulmonary nodules from a tertiary oncology follow-up centre. *Clin Radiol* 2017; **72**: 177.e1–177.e8. doi: https://doi.org/10.1016/j.crad.2016.09.014

38. Xu DM, van der Zaag-Loonen HJ, Oudkerk M, Wang Y, Vliegenthart R, Scholten ET, et al. Smooth or attached solid indeterminate nodules detected at baseline CT screening in the Nelson study: Cancer risk during 1 year of follow-up. *Radiology* 2009; **250**: 264–72.

39. Bankier AA, MacMahon H, Goo JM, Rubin GD, Schaefer-Prokop CM, Naidich DP. Recommendations for measuring pulmonary nodules at CT: a statement from the Fleischner Society. *Radiology* 2017; **285**: 584–600. doi: https://doi.org/10.1148/radiol.2017162894

40. Korst RJ, Lee BE, Krinsky GA, Rutledge JR. The utility of automated volumetric growth analysis in a dedicated pulmonary nodule clinic. *J Thorac Cardiovasc Surg* 2011; **142**: 372–7. doi: https://doi.org/10.1016/j.jtcvs.2011.04.015

41. Han D, Heuvelmans MA, Vliegenthart R, Rook M, Dorrius MD, de Jonge GJ, et al. Influence of lung nodule margin on volume- and diameter-based reader variability in CT lung cancer screening. *Br J Radiol* 2018; **91**: 20170405. doi: https://doi.org/10.1259/bjr.20170405

42. Gietema HA, Wang Y, Xu D, van Klaveren RJ, de Koning H, Scholten E, et al. Pulmonary nodules detected at lung cancer screening: interobserver variability of semiautomated volume measurements. *Radiology* 2006; **241**: 251–7. doi: https://doi.org/10.1148/radiol.2411050860

43. Ko JP, Berman EJ, Kaur M, Babb JS, Bomsztyk E, Greenberg AK, et al. Pulmonary nodules: growth rate assessment in patients by using serial CT and three-dimensional volumetry. *Radiology* 2012; **262**: 662–71. doi: https://doi.org/10.1148/radiol.11100878

44. Revel M-P, Merlin A, Peyrard S, Triki R, Couchon S, Chatellier G, et al. Software volumetric evaluation of doubling times for differentiating benign versus malignant pulmonary nodules. *AJR Am J Roentgenol* 2006; **187**: 135–42. doi: https://doi.org/10.2214/AJR.05.1228

45. Christe A, Torrente JC, Lin M, Yen A, Hallett R, Roychoudhury K, et al. CT screening and follow-up of lung nodules: effects of tube current-time setting and nodule size and density on detectability and of tube current-time setting on apparent size. *AJR Am J Roentgenol* 2011; **197**: 623–30.

46. Gartenschläger M, Schweden F, Gast K, Westermeier T, Kauczor H, von Zitzewitz H, et al. Pulmonary nodules: detection with low-dose vs conventional-dose spiral CT. *Eur Radiol* 1998; **8**: 609–14.

47. Karabulut N, Törü M, Gelebek V, Gülsün M, Ariyürek OM. Comparison of low-dose and standard-dose helical CT in the evaluation of pulmonary nodules. *Eur Radiol* 2002; **12**: 2764–9.

48. Fischbach F, Knollmann F, Griesshaber V, Freund T, Akkol E, Felix R. Detection of pulmonary nodules by multislice computed tomography: improved detection rate with reduced slice thickness. *Eur Radiol* 2003; **13**: 2378–83.

49. Lee HY, Goo JM, Lee HJ, Lee CH, Park CM, Park E-A, et al. Usefulness of concurrent reading using thin-section and thick-section CT images in subcentimetre solitary pulmonary nodules. *Clin Radiol* 2009; **64**: 127–32.

50. Sinsuat M, Saita S, Kawata Y, Niki N, Ohmatsu H, Tsuchida T, et al. Influence of slice thickness on diagnoses of pulmonary nodules using low-dose CT: potential dependence of detection and diagnostic agreement on features and location of nodule. *Acad Radiol* 2011; **18**: 594–604.

51. Cui Y, Ma D-Q, Liu W-H. Value of multiplanar reconstruction in MSCT in demonstrating the relationship between solitary pulmonary nodule and bronchus. *Clin Imaging* 2009; **33**: 15–21.

52. Diederich S, Lentschig MG, Overbeck TR, Wormanns D, Heindel W. Detection of pulmonary nodules at spiral CT: comparison of maximum intensity projection sliding slabs and single-image reporting. *Eur Radiol* 2001; **11**: 1345–50.

53. Gruden JF, Ouanounou S, Tigges S, Norris SD, Klausner TS. Incremental benefit of maximum-intensity-projection images on observer detection of small pulmonary nodules revealed by multidetector CT. *AJR Am J Roentgenol* 2002; **179**: 149–57.

54. Jankowski A, Martinelli T, Timsit JF, Brambilla C, Thony F, Coulomb M, et al. Pulmonary nodule detection on MDCT images: evaluation of diagnostic performance using thin axial images, maximum intensity projections, and computer-assisted detection. *Eur Radiol* 2007; **17**: 3148–56.

55. Kawel N, Seifert B, Luetolf M, Boehm T. Effect of slab thickness on the CT detection of pulmonary nodules: use of sliding thin-slab maximum intensity projection and volume rendering. *AJR Am J Roentgenol* 2009; **192**: 1324–9.

56. Horeweg N, Scholten ET, de Jong PA, van der Aalst CM, Weenink C, Lammers J-WJ, et al. Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers. *Lancet Oncol* 2014; **15**: 1342–50. doi: https://doi.org/10.1016/S1470-2045(14)70387-0

57. Henschke CI, Yankelevitz DF, Yip R, Reeves AP, Farooqi A, Xu D, et al. Lung cancers diagnosed at annual CT screening: volume doubling times. *Radiology* 2012; **263**: 578–83. doi: https://doi.org/10.1148/radiol.12102489

58. Deppen SA, Blume JD, Kensinger CD, Morgan AM, Aldrich MC, Massion PP, et al. Accuracy of FDG-PET to diagnose lung cancer in areas with infectious lung disease: a meta-analysis. *JAMA* 2014; **312**: 1227–36. doi: https://doi.org/10.1001/jama.2014.11488

59. Ambrosini V, Nicolini S, Caroli P, Nanni C, Massaro A, Marzola MC, et al. PET/CT imaging in different types of lung cancer: an overview. *Eur J Radiol* 2012; **81**: 988–1001. doi: https://doi.org/10.1016/j.ejrad.2011.03.020

60. Fletcher JW, Kymes SM, Gould M, Alazraki N, Coleman RE, Lowe VJ, et al. A comparison of the diagnostic accuracy of 18F-FDG PET and CT in the characterization of solitary pulmonary nodules. *J Nucl Med* 2008; **49**: 179–85. doi: https://doi.org/10.2967/jnumed.107.044990

61. Vansteenkiste JF, Stroobants SG, Dupont PJ, De Leyn PR, De Wever WF, Verbeken EK, et al. FDG-PET scan in potentially operable non-small cell lung cancer: do anatometabolic PET-CT fusion images improve the localisation of regional lymph node metastases? The Leuven lung Cancer Group. *Eur J Nucl Med* 1998; **25**: 1495–501. doi: https://doi.org/10.1007/s002590050327

62. McWilliams A, Tammemagi MC, Mayo JR, Roberts H, Liu G, Soghrati K, et al. Probability of cancer in pulmonary nodules detected on first screening CT. *N Engl J Med Overseas Ed* 2013; **369**: 910–9. doi: https://doi.org/10.1056/NEJMoa1214726

63. Henschke CI, Yankelevitz DF, Mirtcheva R, McGuinness G, McCauley D, Miettinen OS, et al. CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. *AJR Am J Roentgenol* 2002;

178: 1053–7. doi: https://doi.org/10.2214/ajr.178.5.1781053

64. Matsuguma H, Mori K, Nakahara R, Suzuki H, Kasai T, Kamiyama Y, et al. Characteristics of subsolid pulmonary nodules showing growth during follow-up with CT scanning. *Chest* 2013; **143**: 436–43. doi: https://doi.org/10.1378/chest.11-3306

65. Ichinose J, Kohno T, Fujimori S, Harano T, Suzuki S, Fujii T. Invasiveness and malignant potential of pulmonary lesions presenting as pure ground-glass opacities. *Annals of Thoracic and Cardiovascular Surgery* 2014; **20**: 347–52. doi: https://doi.org/10.5761/atcs.oa.13-00005

66. J-Y O, Kwon S-Y, Yoon H-I, Lee SM, Yim J-J, Lee J-H, et al. Clinical significance of a solitary ground-glass opacity (GGO) lesion of the lung detected by chest CT. *Lung Cancer Amst Neth* 2007; **55**: 67–73.

67. Lee SM, Park CM, Goo JM, Lee CH, Lee HJ, Kim KG, et al. Transient part-solid nodules detected at screening thin-section CT for lung cancer: comparison with persistent part-solid nodules. *Radiology* 2010; **255**: 242–51. doi: https://doi.org/10.1148/radiol.09090547

68. Lee SH, Lee SM, Goo JM, Kim K-G, Kim YJ, Park CM. Usefulness of texture analysis in differentiating transient from persistent part-solid nodules(PSNs): a retrospective study. *PLoS One* 2014; **9**: e85167. doi: https://doi.org/10.1371/journal.pone.0085167

69. Lee SW, Leem C-S, Kim TJ, Lee KW, Chung J-H, Jheon S, et al. The long-term course of ground-glass opacities detected on thin-section computed tomography. *Respir Med* 2013; **107**: 904–10. doi: https://doi.org/10.1016/j.rmed.2013.02.014

70. Kobayashi Y, Sakao Y, Deshpande GA, Fukui T, Mizuno T, Kuroda H, et al. The association between baseline clinical–radiological characteristics and growth of pulmonary nodules with ground-glass opacity. *Lung Cancer* 2014; **83**: 61–6. doi: https://doi.org/10.1016/j.lungcan.2013.10.017

71. Matsuguma H, Yokoi K, Anraku M, Kondo T, Kamiyama Y, Mori K, et al. Proportion of ground-glass opacity on high-resolution computed tomography in clinical T1 N0 M0 adenocarcinoma of the lung: a predictor of lymph node metastasis. *J Thorac Cardiovasc Surg* 2002; **124**: 278–84. doi: https://doi.org/10.1067/mtc.2002.122298

72. Patz EF, Pinsky P, Gatsonis C, Sicks JD, Kramer BS, Tammemägi MC, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. *JAMA Intern Med* 2014; **174**: 269–74. doi: https://doi.org/10.1001/jamainternmed.2013.12738

73. Yankelevitz DF, Yip R, Smith JP, Liang M, Liu Y, Xu DM, , et al. CT screening for lung cancer: Nonsolid nodules in baseline and annual repeat rounds. *Radiology* 2015; **277**: 555–64. doi: https://doi.org/10.1148/radiol.2015142554

74. Tsutani Y, Miyata Y, Nakayama H, Okumura S, Adachi S, Yoshimura M, et al. Appropriate Sublobar resection choice for ground glass Opacity-Dominant clinical stage Ia lung adenocarcinoma. *Chest* 2014; **145**: 66–71. doi: https://doi.org/10.1378/chest.13-1094

75. Iwata H, Shirahashi K, Mizuno Y, Yamamoto H, Takemura H. Feasibility of segmental resection in non-small-cell lung cancer with ground-glass opacity. *Eur J Cardiothorac Surg* 2014; **46**: 375–9. doi: https://doi.org/10.1093/ejcts/ezu021

76. Yano M, Yoshida J, Koike T, Kameyama K, Shimamoto A, Nishio W, et al. Survival of 1737 lobectomy-tolerable patients who underwent limited resection for cStage Ia non-small-cell lung cancer. *Eur J Cardiothorac Surg* 2015; **47**: 135–42. doi: https://doi.org/10.1093/ejcts/ezu138

77. Fontaine-Delaruelle C, Souquet P-J, Gamondes D, Pradat E, De Leusse A, Ferretti GR, et al. Negative predictive value of transthoracic core-needle biopsy: a multicenter study. *Chest* 2015; **148**: 472–80. doi: https://doi.org/10.1378/chest.14-1907

78. Kothary N, Lock L, Sze DY, Hofmann LV. Computed tomography-guided percutaneous needle biopsy of pulmonary nodules: impact of nodule size on diagnostic accuracy. *Clin Lung Cancer* 2009; **10**: 360–3. doi: https://doi.org/10.3816/CLC.2009.n.049

79. Wallace MJ, Krishnamurthy S, Broemeling LD, Gupta S, Ahrar K, Morello FA, et al. CT-guided percutaneous fine-needle aspiration biopsy of small. *Radiology* 2002; **225**: 823–8.

80. Ohno Y, Hatabu H, Takenaka D, Higashino T, Watanabe H, Ohbayashi C, et al. CT-guided transthoracic needle aspiration biopsy of small. *AJR Am J Roentgenol* 2003; **180**: 1665–9.

81. Tsukada H, Satou T, Iwashima A, Souma T. Diagnostic accuracy of CT-guided automated needle biopsy of lung nodules. *AJR Am J Roentgenol* 2000; **175**: 239–43. doi: https://doi.org/10.2214/ajr.175.1.1750239

82. Choi SH, Chae EJ, Kim J-E, Kim EY, Oh SY, Hwang HJ, et al. Percutaneous CT-guided aspiration and core biopsy of pulmonary nodules smaller than 1 cm: analysis of outcomes of 305 procedures from a tertiary referral center. *AJR Am J Roentgenol* 2013; **201**: 964–70. doi: https://doi.org/10.2214/AJR.12.10156

83. Gupta S, Krishnamurthy S, Broemeling LD, Morello FA, Wallace MJ, Ahrar K, et al. Small (</=2-cm) subpleural pulmonary lesions: short- versus long-needle-path CT-guided Biopsy--comparison of diagnostic yields and complications. *Radiology* 2005; **234**: 631–7. doi: https://doi.org/10.1148/radiol.2342031423

84. De Filippo M, Saba L, Concari G, Nizzoli R, Ferrari L, Tiseo M, et al. Predictive factors of diagnostic accuracy of CT-guided transthoracic fine-needle aspiration for solid noncalcified, subsolid and mixed pulmonary nodules. *Radiol Med* 2013; **118**: 1071–81. doi: https://doi.org/10.1007/s11547-013-0965-4

85. Jin KN, Park CM, Goo JM, Lee HJ, Lee Y, Kim JI, et al. Initial experience of percutaneous transthoracic needle biopsy of lung nodules using C-arm cone-beam CT systems. *Eur Radiol* 2010; **20**: 2108–15. doi: https://doi.org/10.1007/s00330-010-1783-x

86. Choi JW, Park CM, Goo JM, Park Y-K, Sung W, Lee H-J, et al. C-arm cone-beam CT-guided percutaneous transthoracic needle biopsy of small (≤ 20 Mm) lung nodules: diagnostic accuracy and complications in 161 patients. *AJR Am J Roentgenol* 2012; **199**: W322–W330. doi: https://doi.org/10.2214/AJR.11.7576

87. Choo JY, Park CM, Lee NK, Lee SM, Lee H-J, Goo JM. Percutaneous transthoracic needle biopsy of small (≤ 1 cm) lung nodules under C-arm cone-beam CT virtual navigation guidance. *Eur Radiol* 2013; **23**: 712–9. doi: https://doi.org/10.1007/s00330-012-2644-6

88. Ohno Y, Hatabu H, Takenaka D, Imai M, Ohbayashi C, Sugimura K. Transthoracic CT-guided biopsy with multiplanar reconstruction image improves diagnostic accuracy of solitary pulmonary nodules. *Eur J Radiol* 2004; **51**: 160–8. doi: https://doi.org/10.1016/S0720-048X(03)00216-X

89. Wiener RS, Schwartz LM, Woloshin S, Welch HG. Population-based risk for complications after transthoracic needle lung biopsy of a pulmonary nodule: an analysis of discharge records. *Ann Intern Med* 2011; **155**: 137–44. doi: https://doi.org/10.7326/0003-4819-155-3-201108020-00003

90. van 't Westeinde SC, Horeweg N, Vernhout RM, Groen HJM, Lammers J-WJ, Weenink C, et al. The role of conventional bronchoscopy in the workup of suspicious CT scan screen-detected pulmonary nodules. *Chest* 2012; **142**: 377–84. doi: https://doi.org/10.1378/chest.11-2030

91. Baaklini WA, Reinoso MA, Gorin AB, Sharafkaneh A, Manian P. Diagnostic yield of fiberoptic bronchoscopy in evaluating solitary pulmonary nodules. *Chest* 2000; **117**: 1049–54. doi: https://doi.org/10.1378/chest.117.4.1049

92. Aoshima M, Chonabayashi N. Can HRCT contribute in decision-making on indication for flexible bronchoscopy for solitary pulmonary nodules and masses? *Journal of Bronchology* 2001; **8**: 161–5. doi: https://doi.org/10.1097/00128594-200107000-00002

93. Schwarz C, Schönfeld N, Bittner RC, Mairinger T, Rüssmann H, Bauer TT, et al. Value of flexible bronchoscopy in the pre-operative work-up of solitary pulmonary nodules. *Eur Respir J* 2013; **41**: 177–82. doi: https://doi.org/10.1183/09031936.00018612

94. Ali MS, Trick W, Mba BI, Mohananey D, Sethi J, Musani AI. Radial endobronchial ultrasound for the diagnosis of peripheral pulmonary lesions: a systematic review and meta-analysis. *Respirology* 2017; **22**: 443–53. doi: https://doi.org/10.1111/resp.12980

95. Gex G, Pralong JA, Combescure C, Seijo L, Rochat T, Soccal PM. Diagnostic yield and safety of electromagnetic navigation bronchoscopy for lung nodules: a systematic review and meta-analysis. *Respiration* 2014; **87**: 165–76. doi: https://doi.org/10.1159/000355710

96. Heo EY, Lee KW, Jheon S, Lee J-H, Lee C-T, Yoon HI. Surgical resection of highly suspicious pulmonary nodules without a tissue diagnosis. *Jpn J Clin Oncol* 2011; **41**: 1017–22. doi: https://doi.org/10.1093/jjco/hyr073

97. Sihoe ADL, Hiranandani R, Wong H, Yeung ESL. Operating on a suspicious lung mass without a preoperative tissue diagnosis: pros and cons. *Eur J Cardiothorac Surg* 2013; **44**: 231–7. doi: https://doi.org/10.1093/ejcts/ezs671