Management of pulmonary nodules

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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.

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. The definition used by guidelines has also included nodules in contact with the pleura but excludes those associated with lymphadenopathy or pleural disease. Nodules are further categorised by their appearance into solid nodules and subsolid 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.

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%. Lung cancer screening programmes have predominantly 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%. 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. 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. 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. 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%. The most common histological findings following resection of a benign lesion were granulomas, chondromas/hamartomas, intrapulmonary lymph nodes,
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 primaries15,16 or metastatic disease17 are more common. Larger nodule size, distance from the pleural margin, multiple 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 cancers19 or where nodules were >10 mm in diameter.17 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 guidelines1 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 mm³ 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 mm³ 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.
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. Further studies examining the histological correlates of these lesions confirmed that those with the typical radiological findings were confirmed intrapulmonary lymph nodes on sampling. 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.

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 factors include:

- **Smooth border**: The presence of a smooth border is associated with a greater risk of malignancy.
- **Satellite nodules**: The presence of satellite nodules is also associated with a greater risk of malignancy.
- **Calcification**: The presence of calcification is associated with a lower risk of malignancy.
- **Peri-fissural location**: Nodules located near to fissures are associated with a greater risk of malignancy.
- **Size and growth rate**: Larger nodules or those that grow quickly are associated with a greater risk of malignancy.
- **Patient factors**: Factors such as age, smoking history, and family history of lung cancer can also influence the risk of malignancy.

*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.*
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 mm³ 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.38,39 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 ≥800 mm³ 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, gives 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.3,40,41 Gieta et al32 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 known heterogeneity in this subtype.
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 mm³ with a risk of malignancy >10% followed by further assessment with the Herder model.

The majority of lung cancers show 18fluodeoxyglucose (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
nodules. 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. 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. The ELCAP trial reported an overall prevalence of 2.8% for pGGNs and 1.6% for PSNs. The histological correlates of these include atypical adenomatous hyperplasia, adenocarcinoma-in-site, minimally invasive adenocarcinoma and invasive adenocarcinoma. Whilst the majority of SSNs are benign, the risk is increased in PSNs, particularly larger lesions and those with growth of more than 2 cm during follow up. 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.

Up to a third of SSNs may resolve after a 3 month period of surveillance; 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. 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. 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. 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. 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. 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 sublobar resection of SSNs is good with low operative mortality and low risk of recurrence.

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).

Figure 6. Spiculate node left upper lobe nodule (a) with intense 18FDF uptake on PET-CT (b). 18FDG, 18-fludeoxyglucose; PET, positron emission tomography.
**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 biopsy**

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, although high sensitivity and specificity is still reported in case series of nodules <10 mm undergoing biopsy. A long needle tract may also reduce diagnostic accuracy or the ability to obtain adequate samples for analysis. PSNs and pGGNs in particular have been shown to have a lower diagnostic accuracy than solid nodules. The use of cone beam CT to provide real time fluoroscopic images and multiplanar reformattting have been associated with increased diagnostic accuracy.

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%). Low FEV1, 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 sub-study 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.

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