

Diagnostic Imaging Pathways - Solid Pulmonary Nodules

Population Covered By The Guidance

This pathway provides guidance on the imaging surveillance of adult patients with solid pulmonary nodules

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Quick User Guide

Move the mouse cursor over the **PINK** text boxes inside the flow chart to bring up a pop up box with salient points.

Clicking on the **PINK** text box will bring up the full text.

The relative radiation level (RRL) of each imaging investigation is displayed in the pop up box.

SYMBOL	RRL	EFFECTIVE DOSE RANGE
	None	0
	Minimal	< 1 millisieverts
	Low	1-5 mSv
	Medium	5-10 mSv
	High	>10 mSv

Pathway Diagram

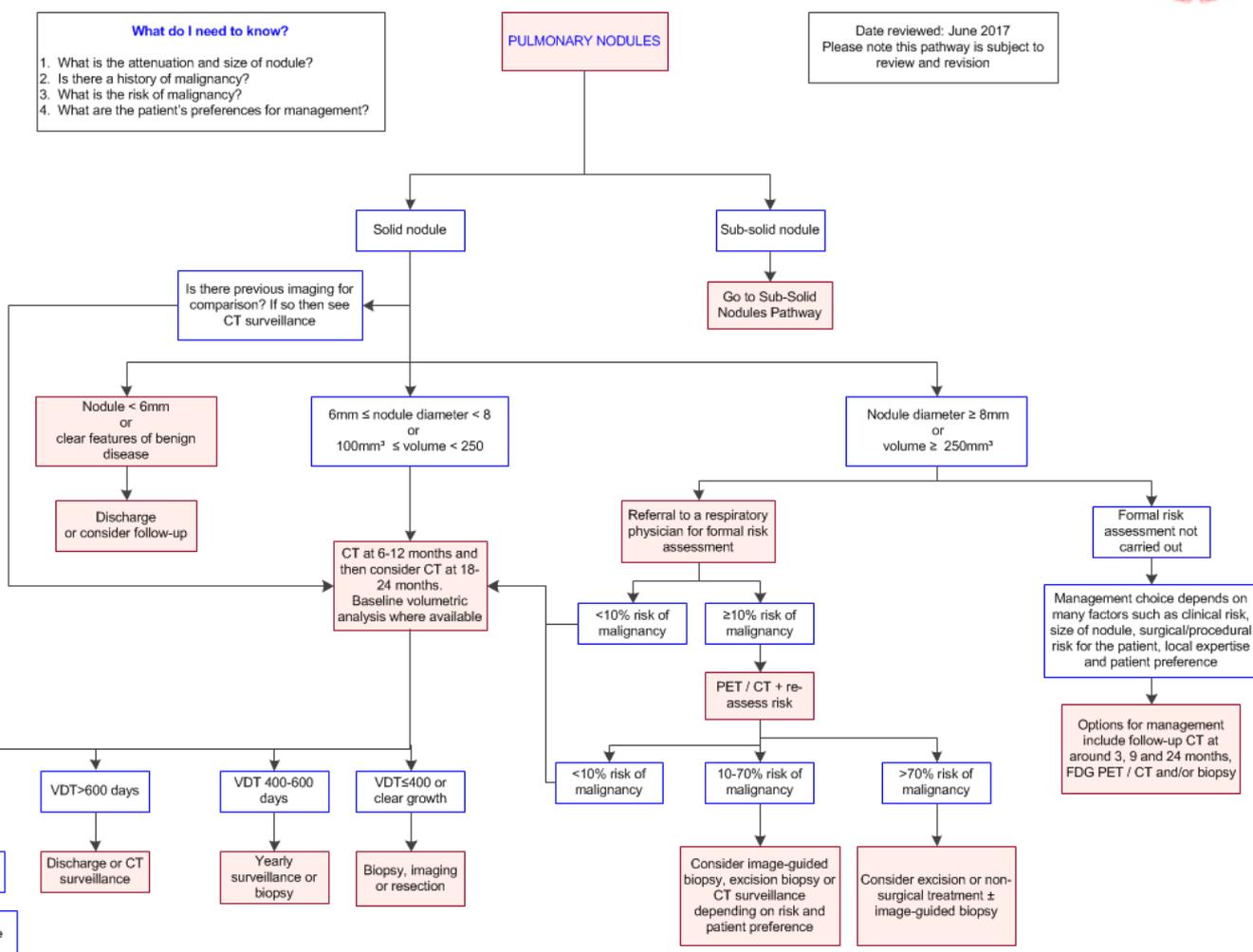


Image Gallery

Note: These images open in a new page

1



Solitary Pulmonary Nodule

Image 1 (Plain radiograph): There is a well circumscribed opacity in the left upper lung zone with punctate calcification (arrow). The appearances are in keeping with a pulmonary hamartoma.

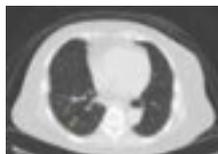
2



Solitary Pulmonary Nodule

Image 2 (Plain Radiograph): There is a circumscribed mass arising from the right hilum with spotty calcification (arrow). Biopsy confirmed a bronchial carcinoid tumour.

3



Solitary Pulmonary Nodule

Image 3 (Computed Tomography): A non-calcified 7mm soft tissue density nodule is located in the right lower lobe.

Teaching Points

- A pulmonary nodule is radiologically defined as an opacity <3cm in diameter with no associated atelectasis or lymphadenopathy
- This pathway presents an approach to the investigation and management of solid pulmonary nodules that are detected incidentally or through lung screening programs. This guide may be applied to patients with a history of malignancy, considering that the presence of previous malignancy is likely to increase the probability that a nodule is malignant
- Management of pulmonary nodules should be guided by the risk of malignancy according to patient factors and nodule characteristics
- Risk prediction models such as the Brock and Herder models have been externally validated and are a useful tool for estimating risk of malignancy. Risk assessment should be carried out by a respiratory physician
- Volumetric analysis of nodule growth is preferred over manual measurements and allows a faster and more reliable diagnosis
- Several image-guided biopsy techniques are available and the choice depends on local expertise, availability, location of nodule and patient pReferences

Pulmonary Nodules

- A pulmonary nodule is radiologically defined as an intra-parenchymal rounded or irregular opacity less than 3cm in diameter and not associated with atelectasis or lymphadenopathy. Lesions that are larger than this are generally referred to as masses and are more likely to be malignant [1](#)
- Pulmonary nodules can be further classified according to their attenuation on computed tomography (CT). A solid nodule has homogenous soft-tissue attenuation. Sub-solid nodules include ground-glass nodules (focal area of hazy increased attenuation through which bronchovascular margins can be visualised) and part-solid nodules (consisting of both solid soft-tissue attenuation and ground-glass components) [1](#)
- The widespread use of multi-detector CT has made it commonplace to detect pulmonary nodules often when they are subcentimetre in size. Nodules may be detected incidentally (on chest radiographs, chest CT or imaging for other purposes) or in some countries, through lung screening programs. The majority of these nodules have a benign aetiology but a small proportion represent malignancy and if detected early, may be cured
- The primary aim of investigation is to determine which nodules are malignant early whilst minimising patient exposure to ionising radiation and limiting the number of unnecessary invasive procedures
- This pathway presents an evidence-based and consensus-based approach to the investigation and management of solid pulmonary nodules that are detected incidentally or through lung screening programs
- Some studies have demonstrated that a history of malignancy increases the overall probability that an individual nodule is malignant (either primary lung cancer or metastasis). [2, 3](#) However, there is insufficient evidence to recommend a different diagnostic approach to nodules detected incidentally or through screening. Therefore, this pathway can be used to assess the risk of nodules in patients with a history of malignancy while taking in to consideration the presence of previous malignancy as a risk factor [4, 5](#)
- Assessing the risk of malignancy, as related to patient factors (age, smoking status) and nodule characteristics on CT (such as size, growth rate, upper lobe location) and/or PET is essential to

guiding investigation and management of lung nodules [5](#)

Features Suggestive of Benign Disease

- The size of a nodule has a strong effect on predicting the risk of malignancy [4, 5](#)
- In the National Lung Screening Trial (NLST) of asymptomatic high-risk patients who underwent lung cancer screening with low-dose CT, the positive predictive value (PPV) for malignancy increased as nodule size increased (PPV for 4-6mm nodules was 0.3% and increased to 17.5% for 21-30mm nodules) [6](#)
- In the Dutch-Belgian CT screening trail (NELSON), the risk of malignancy after 2 years of nodules < 5mm (or volume < 100mm³) was no different to participants without nodules, indicating that nodules < 5mm, even in a high-risk screening population, carries little, if any additional risk [7](#)
- Recent guidelines recommend discharging patients with nodules < 6mm in maximum diameter (or < 100mm³ volume) [4, 5](#)
- Although this recommendation may lead to a small proportion of people with malignant nodules being discharged (estimated <0.5%), this risk is thought to be outweighed by the harm from continuing radiation exposure through follow-up [4](#)
- The presence of diffuse, central, laminated or popcorn pattern calcification (odds ratio 0.09-0.20) and perifissural location are also predictors of benign aetiology [4](#)
- Typical perifissural nodules (PFNs) are homogenously solid nodules with smooth margins attached to a fissure with an oval, lentiform or triangular shape. Atypical PFNs meet the criteria of typical PFNs but are not visibly attached to a fissure. [8](#) Both typical and atypical PFNs are thought to be benign and do not require further follow-up [4](#)
- In a subset analysis of PFNs detected in the NELSON trial, of the 794 PFNs detected at baseline screening, none developed into cancer after 5.5 years of follow-up. [8](#) Only one PFN was resected in this series and it proved to be a lymph node
- PFNs may enlarge despite being benign, with growth seen in 15.5% of typical PFNs and in 16% of atypical PFNs [8](#)

Risk Prediction Models

- The clinical and radiological predictors of malignancy that have consistently been identified in high quality studies are [4](#)
 - Age (odds ratio 1.04-2.2 for every 10 year increment) [9](#)
 - Current or former smoking status (odds ratio 2.2-7.9)
 - Pack-years of smoking
 - Previous history of extra-pulmonary cancer
 - Nodule diameter (odds ratio approximately 1.1 for each 1mm increment) [9](#)
 - Spiculation (odds ratio 2.1-5.7)
 - Upper lobe location
 - Pleural indentation
 - Volume doubling time
- Several quantitative prediction models which combine clinical and radiological factors have been described to assess the likelihood of malignancy in pulmonary nodules [2, 9-12](#)
- One study that compared the accuracy of a clinical prediction model and physicians' individual clinical judgement at determining the risk of malignancy of pulmonary nodules found no significant difference between the two methods, however further analysis found that physicians overestimated the probability of malignancy in patients with a low risk of malignant disease [13](#)

- Recent guidelines recommend the use of the Brock model (full version including speculation as a parameter) for initial assessment of pulmonary nodules ($\geq 8\text{mm}$ or $\geq 300\text{mm}^3$) at presentation in people aged ≥ 50 or who are smokers or former smokers [4](#)
- The Brock University model was developed in a Canadian lung cancer screening cohort consisting of current or former smokers between 50 and 75 years of age without a history of lung cancer. [11](#) Several models were developed by combining the predictors for cancer found in this cohort, which included
 - Older age
 - Female sex
 - Family history of lung cancer
 - Emphysema
 - Larger nodule size
 - Location of the nodule in the upper lobe
 - Part-solid nodule type
 - Lower nodule count
 - Spiculation
- The predictive models were applied to a cohort of patients undergoing low-dose CT screening as part of chemoprevention trials and showed excellent discrimination between benign and malignant nodules with AUCs of over 0.90, even in subcentimetre nodules for which management decisions are most challenging [11](#)
- The full Brock model with spiculation has since been externally validated in a UK setting and has a higher accuracy for predicting malignancy than older models, with an AUC of 0.90 (95% CI 0.86 to 0.95) [14](#)
- Recommendations for subsequent imaging and management are guided by the calculated risk of malignancy, with nodules at low risk of malignancy proceeding to CT surveillance and those at high risk proceeding to nuclear imaging [4, 15, 16](#)
- There is no current consensus as to the definition of the thresholds for risk, with some guidelines quoting $\geq 10\%$ as high risk [4](#) and others quoting $> 65\%$. [15](#) Thresholds are based on balancing the risks of harm due to interventions such as percutaneous/ excision biopsy against the risk of stage progression of lung cancer during CT surveillance (for which no published estimates are currently available). The predicted probability of malignancy also varies greatly with the risk prediction model used. [4](#) When using the Brock model, a threshold of 10% has been recommended
- The applicability of the Brock model to patients outside the scope of those included in the development and validation cohorts is less reliable
- Generally, the initial risk assessment in patients who have multiple solid pulmonary nodules should be determined on the largest nodule [4, 7](#)

Thin Section Computed Tomography (CT)

- CT with the thinnest slices possible is the initial investigation of choice for the evaluation of pulmonary nodules [5, 15, 16](#)
- Firstly, it can distinguish true lung nodules from lesions of the chest wall, pleura and imaging artefact [17](#)
- Secondly, it can identify features that suggest a benign or malignant process such as
 - Calcification pattern: diffuse, central and laminated calcification which are highly suggestive of a benign lesion [4](#)
 - The presence of fat: highly suggestive of a benign lesion [18, 19](#)
 - Large nodule diameter is suggestive of malignancy (odds ratio approximately 1.1 for each 1mm increment) [9, 16, 20](#)
 - Upper lobe location is independently associated with malignancy



- Spiculation is independently associated with malignancy (odds ratio 2.1-5.7)
- Synchronous lung lesions, enlarged lymph nodes or metastatic liver and adrenal lesions that all suggest a malignant lesion
- Surveillance strategies utilising CT have been developed for the follow-up of patients with low risk pulmonary nodules. [4](#), [15](#), [16](#). The aim of such strategies is to use the assessment of nodule growth to discriminate between benign and malignant nodules
- Stability over 2 years of follow-up has traditionally been regarded as indicative of benign disease; however recent guidelines suggest that 2 years may not be necessary in all cases. The traditional recommendation of 2-year follow up was based on studies with thick CT sections or chest radiographs and was made before the important differences between solid and subsolid nodules were recognized [3](#), [5](#), [15](#), [16](#)

Nodule Growth and Volumetric Analysis

- Traditionally, the size of a pulmonary nodule has been assessed by obtaining the average of the diameters in the transverse plane. [16](#), [21](#). Assessment of growth is estimated by calculating the volume doubling time (VDT) of a nodule, which compares this measurement with the baseline nodule diameter for the given time interval between scans [22](#)
- This manual method of calculating VDT uses an exponential growth model that assumes uniform three-dimensional tumour growth, hence asymmetric growth may not be detected with two-dimensional measurements [23](#)
- Two-dimensional measurements have been found to be unreliable for assessing nodule growth, with significant intrareader and interreader variability for measurements [24](#)
- Computer-assisted techniques (semi-automated and automated volumetric analysis) based on segmentation of nodules in thin-section CT have been developed for assessing volume growth
- Several advantages of volumetric measurements of growth have been described including
 - Greater sensitivity when compared to manual diameter-change measurements (91% vs 54% respectively) [5](#), [25](#)
 - Demonstrates growth consistent with malignancy at an earlier time point compared to calliper measurements [26](#)
 - Low interobserver variability and low-moderate interscan variability, [27](#), [28](#), with less reported interscan variability for larger nodules [29](#)
 - Has the potential to change management decisions and prompt biopsy [30](#)
 - Volumetry allows a more confident assessment of nodule stability, which allows earlier discharge during surveillance [3](#)
- Some limitations of volumetric analysis of nodule growth include
 - Incomplete and variable segmentation of nodules with irregular margins or shape [31](#)
 - Differences in segmentation performance of the available semi-automated software packages [29](#)
- Recent guidelines recommend automated volumetric measurements for assessment of nodule growth, where available with ongoing management guided by VDT [3-5](#)
- VDT for solid nodules are well established with a large majority of times being in the 100–400-day range [5](#)
- In one large trial which determined the 2 year risk of lung cancer according to volumetry-derived VDT in high-risk patients undergoing low-dose CT screening, patients with nodule VDTs of < 400 days or 400-600 days had significantly increased risk of lung cancer compared to patients with no nodules (9.9% and 4.0% risk respectively, $P < 0.0001$ for both). [32](#). Patients with slower growing nodules (VDT > 600 days) and those with unchanged nodules after 12 months did not have a statistically significant increased risk of lung cancer (0.8% and 0.7% risk respectively)

Positron Emission Tomography / Computed Tomography (PET / CT)

- PET imaging uses the uptake of 18-fluorodeoxyglucose (FDG) to measure glucose metabolism. Increased uptake is demonstrated in cells with a high metabolic rate such as tumours and areas of infection and inflammation
- Early studies of diagnostic accuracy, which focused on FDG-PET alone, reported high sensitivities and moderate-high specificities for characterisation of malignant versus benign pulmonary nodules (95% and 82% respectively in one meta-analysis) [33](#)
- Integrated PET / CT scanners which provide functional and anatomical information are now widely available and FDG-PET / CT is routinely used in the management of lung cancer [34](#)
- Recent guidelines recommend further assessment of solid pulmonary nodules with an initial risk > 10% (Brock model) with PET / CT [4](#)
- Studies have confirmed the superiority of integrated PET / CT for further characterisation of solid nodules over PET alone [22, 35, 36](#)
- The diagnostic accuracy of PET / CT has been studied in a number of lung cancer screening cohorts, and high sensitivity, specificity and diagnostic accuracies have been reported [37, 39](#)
- Quantitative analysis of FDG avidity has not been shown to provide additional benefit over qualitative visual assessment [3, 40](#)
- Herder et al demonstrated a significant improvement in accuracy of an older risk prediction model following incorporation of FDG uptake on PET imaging, as scored qualitatively using a four-point scale (0, absent; 1, faint; 2, moderate or 3, intense) with an increase in the area under the ROC curve from 0.79 to 0.92 ($p < 0.0003$). [12](#) In a validation study of four prediction models and their accuracy at predicting the likelihood of malignancy, the Herder model had significantly higher accuracy than the other three models and accuracy remained high when tested on patients outside the original model inclusion criteria [14](#)
- These findings have been incorporated into recent guidelines, which recommend qualitative assessment of PET / CT with the four-point scale describer by Herder et al and re-assessment of risk after PET / CT using the Herder prediction tool [4](#)
- There is limited evidence to guide practice on the ability of PET / CT to characterise sub-centimetre nodules. The largest case series to date of nodules < 10mm reported a sensitivity of 83% and specificity of 100% but included only 44 patients. [38](#) Many PET / CT scanners in current use are unable to assess nodules < 8 mm in diameter due to spatial resolution of the system and image pixel size. [3, 4](#) This threshold may fall with advances in technology

Non-Surgical Biopsy

- The options for management of pulmonary nodules once imaging tests have been performed include surgical resection, non-surgical biopsy and CT surveillance [4, 15, 16](#)
- Surgical resection is the diagnostic gold standard for nodules with a high likelihood of malignancy on non-invasive imaging and the definitive treatment of malignant nodules
- Non-surgical biopsy (bronchoscopy or image-guided) or CT surveillance are used where there is insufficient certainty about the diagnosis to allow definitive management
- There are advantages and disadvantages to each approach and the choice of test depends of several factors including the likelihood of malignancy, the size and location of the nodule, surgical/procedural risk for the patient, local expertise and the patient's preferences for management [5](#)

Bronchoscopy

- The sensitivity and negative predictive value of conventional bronchoscopy for detecting malignancy in suspicious nodules is low (13.5% and 47.6% respectively) [41](#)
- Diagnostic yield is increased when bronchoscopy is combined with guided techniques, such as electromagnetic navigation, radial endobronchial ultrasound and fluoroscopy [41, 42](#) and when the CT bronchus sign (the finding that the third or fourth order bronchus leads to the lesion) is present [4, 43](#)
- Despite imaging guidance, the non-diagnostic rate of bronchoscopy is still significant and may result in additional procedures [43](#)
- Bronchoscopy with guidance has a relatively low diagnostic yield for nodules < 20mm and in the peripheral third of the lung [4](#)
- The main complications associated with bronchoscopy are bleeding (2-5%) and pneumothorax (2-4%) [15](#)

Image-Guided Biopsy

- Image-guided biopsy is performed by passing a needle percutaneously through the chest wall into the target nodule. It is usually performed under CT guidance but can be performed with ultrasound, although there is limited high quality evidence on the efficacy of this approach [4](#)
- CT-guided biopsy is generally the preferred approach for peripherally located pulmonary nodules [4](#)
- The diagnostic accuracy of CT-guided is high with a pooled sensitivity of 90% (95% CI 88.8% to 92.4%), specificity 95% (95% CI 91.1% to 96.0%), PPV 97.4% (95% CI 96.2% to 98.3%) and NPV 79.9% (95% CI 76.0% to 83.4%)[4](#)
- Factors that reduce the accuracy of CT-guided biopsy include smaller nodule size [5, 44, 45](#), longer needle path [45](#) and ground-glass morphology [5, 46](#)
- Pneumothorax is the most common complication of CT-guided biopsy and rates reported in the literature vary significantly. The largest cross-sectional analysis to date describing complications following CT-guided biopsy reports the risk of pneumothorax as 15% (95% CI 14.0% to 16.0%), and 6.6% (95% CI 6.0% to 7.2%) of all biopsies resulted in insertion of a chest drain [47](#)
- Factors that increase the risk of pneumothorax include
 - Lower FEV1 [45, 48](#)
 - The presence of emphysema along the needle tract [49](#)
 - Longer needle path length [45](#)
 - Number of punctures [48](#)
 - Upper lobe location of nodule [50](#)
 - Core biopsy vs aspiration [48](#)
- When deciding on CT-guided transthoracic needle biopsy, the risk of pneumothorax should be taken into consideration
- As with any other diagnostic test, the post-test probability is dependent on the pre-test probability and the diagnostic performance of the test. Callister et al described the significance of pre-test probability when considering CT-guided percutaneous biopsy in recent guidelines. [4](#) When pre-test probability of cancer is high (for example 95%), applying an investigation (CT-guided biopsy) with a negative likelihood ratio of 0.10 results in a post-test probability which remains relatively high after negative biopsy (65%). However, with a lower pre-test probability (for example 50%), the post-test probability drops to 9.0%. This suggests that CT-guided biopsy would have the greatest utility in nodules with intermediate pre-test malignancy risk [3, 4](#)
- Negative lung biopsies should be interpreted in the context of the pre-test probability of malignancy [4](#)

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Date of literature search: April 2017

The search methodology is available on request. [Email](#)

References are graded from Level I to V according to the Oxford Centre for Evidence-Based Medicine, Levels of Evidence. [Download the document](#)

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