Diagnosis of the Solitary Pulmonary Nodule

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KEYWORDS

• Solitary pulmonary nodule • Nodule guidelines • Risk stratification • Biomarker
• Diagnostic bronchoscopy

KEY POINTS

- Uptake of lung cancer screening and widespread use of diagnostic computed tomography scans discover an increasing number of nodules requiring evaluation.
- Patient and nodule characteristics help determine malignancy risk, and biomarkers are anticipated to play an important role in improving risk assessment.
- Advancements in navigational and robotic-assisted bronchoscopy aided by enhanced imaging are improving diagnostic yield with fewer complications.

INTRODUCTION

A pulmonary nodule, defined as a discrete density less than 30 mm in size surrounded by aerated lung, is a common radiologic finding presenting a unique challenge to clinicians. Nodules can be classified as solid or subsolid depending on attenuation. Subsolid nodules are further defined as pure ground-glass nodules (GGNs) or part-solid nodules (PSNs; **Figs. 1–3**).

Current data suggest that 29% of diagnostic chest computed tomography (CT) scans demonstrate a nodule, which equates to roughly 1.57 million Americans a year with a nodule identified incidentally.[1] With respect to lung cancer screening (LCS) CT scans, depending on the nodule size cutoff employed, 23% to 51% of participants in LCS trials have a nodule detected on the initial scan.[2–6] Approximately 95% of all incidentally detected nodules are ultimately found to be benign at 2 years.[1] The false-positive rate on an initial LCS CT was reported as 19.8% and 26.3% in the Nederlands Leuvens Screening Onderzoek (NELSON) and National Lung Cancer Screening (NLST) trials, respectively.[7,8]

The differential diagnosis of a lung nodule is broad and includes neoplastic, both infectious and noninfectious inflammatory processes, as well as congenital abnormalities,[9,10] which are detailed in **Box 1**. Establishing a definitive diagnosis of a lung nodule involves assessment of the patient's current and past medical history, nodule characteristics on imaging studies, and risk stratification to determine the likelihood of primary lung cancer.

In 2022, of nearly 20 million new cancer diagnoses, lung cancer had the highest incidence at 12.4%. Lung cancer remains the leading cause of cancer death globally and accounted for 1.8 million deaths or 18.7% of all cancer deaths in 2022.[11,12] Because lung cancer in its early stages can present as a solitary lung nodule, having a thoughtful approach is crucial to ensure a malignant lesion is identified as early as possible to improve outcomes. At the same time, it is imperative to avoid unnecessary testing, procedures, and associated patient anxiety for a benign lesion. This article delves into

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Abbreviations	
ACCP	American College of Chest Physicians
BTS	British Thoracic Society
CBCT	cone beam CT
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CT	computed tomography
CXR	chest radiography
DT	digital tomosynthesis
ENB	electromagnetic navigational bronchoscopy
FDG	18F-fluorodeoxyglucose
GGNs	ground-glass nodules
ICG	indocyanine green
IPF	idiopathic pulmonary fibrosis
LCS	lung cancer screening
LDCT	low-dose CT
Lung-RADS	Lung Imaging Reporting and Data System
NELSON	Nederlands Leuvens Screening Onderzoek
NLST	National Lung Cancer Screening
PSNs	part-solid nodules
PTX	pneumothorax
RAB	robotic-assisted bronchoscopy
rEBUS	radial endobronchial ultrasound
rEBUS-TBB	rEBUS-directed bronchoscopy
ROSE	rapid onsite cytologic examination
SPMs	second primary malignancies
SUV	standardized uptake value
UT	Ultrathin
VDT	volume doubling time

the rapidly developing tools available to clinicians in the management of pulmonary nodules.

Approach to the Diagnosis of a Solitary Pulmonary Nodule

Clinical and radiologic risk assessment for malignancy

Individual-specific risk factors Lung cancer risk is multifactorial, including smoking history, environmental exposures, genetic predisposition, and previous medical history when evaluating individuals with pulmonary nodules.

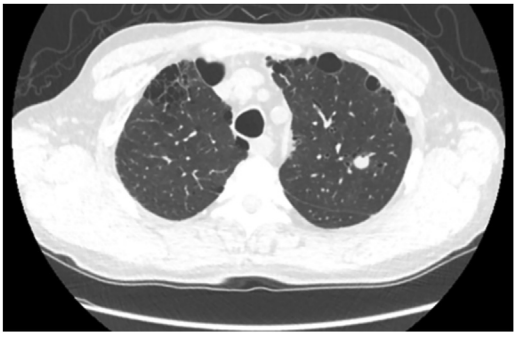

Fig. 1. Left upper lobe, 13 mm, solid nodule.

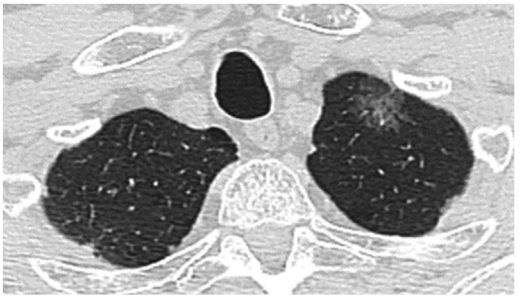

Fig. 2. Left upper lobe, 15 mm, pure ground glass.

Advanced age[13,14] and *smoking history*[14,15] are the most important risk factors for lung cancer. In addition to tobacco use, however, exposure to environmental and occupational lung carcinogens increases the likelihood of lung cancer if there is significant exposure.[16]

Cancer survivors have an 8.1% risk of developing second primary malignancies (SPMs),[17] and lung cancer accounts for up to 17% of SPMs.[18] Cancers associated with developing a second primary lung cancer include lung, head and neck, renal, bladder, and breast cancer treated with radiotherapy.[19–24] Having a first-degree relative with lung cancer is associated with an increased risk of lung cancer, and this association is strongest in women and individuals who have never smoked.[13,25]

Chronic pulmonary diseases have been linked to an increased risk of lung cancer. A case–control study found a 6 fold increase in chronic obstructive pulmonary disease (COPD) among patients diagnosed with lung cancer compared to matched controls by age, sex, and smoking exposure.[26] Similarly, the presence of emphysema increases the likelihood that a lung nodule is malignant,[13] and emphysema detected on CT scans is independently associated with lung cancer, regardless

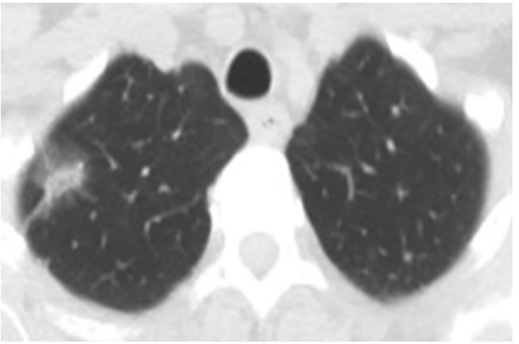

Fig. 3. Right upper lobe, part-solid nodule, 16 mm, 10 mm solid component.

Box 1
Causes of pulmonary nodules

- Neoplasm
  - *Malignant*
    - Primary lung cancer
    - Primary pulmonary lymphoma
    - Carcinoid
    - Metastatic cancer
  - *Benign*
    - Hamartoma
    - Chondroma
    - Lipoma
    - Respiratory papillomatosis
    - Pulmonary benign metastasizing leiomyoma
- Inflammatory
  - *Infectious*
    - Granuloma
    - Mycobacteria (TB and non-TB)
    - Fungi
    - *Nocardia*
    - Rounded pneumonia
    - Septic emboli
    - Lung abscess
    - Hydatid cyst
  - *Noninfectious*
    - Rheumatoid arthritis nodule
    - Granulomatosis with polyangiitis
    - Lymphoid granulomatosis
    - Nodular sarcoid
    - Organizing pneumonia
    - Bronchocele
    - Cryptogenic organizing pneumonia
  - Congenital Abnormalities
    - Arteriovenous malformation
    - Pulmonary venous varix
    - Bronchogenic cyst
    - Bronchial atresia with bronchocele
    - Pulmonary sequestration
- Other
  - Rounded atelectasis
  - Lipoid pneumonia
  - Intrapulmonary lymph node
  - Amyloid
  - Silicosis

Box 2
Clinical features increasing the likelihood that a nodule is malignant

- Advanced age[13,14]
- Smoking history[14,15]
- Occupational and environmental carcinogen Exposure[16]
  - Asbestos
  - Radon
  - Arsenic
  - Beryllium
  - Cadmium
  - Chromium
  - Nickel
  - Crystalline silica
- Prior personal cancer history
  - Lung[19]
  - Head and neck[20]
  - Renal[21]
  - Bladder[22]
  - Breast cancer with prior chest radiation[23,24]
- First-degree relative with lung cancer[13,25]
- Chronic pulmonary disease
  - COPD[26]
  - Emphysema[13,27]
  - IPF[28]

of smoking history.[27] Idiopathic pulmonary fibrosis (IPF) has been shown to be associated with a higher risk of malignancy.[28] A more detailed list of individual-specific factors related to risk for lung cancer is outlined in **Box 2**.

Radiologic-specific findings Imaging findings are central to the appropriate evaluation of lung nodules. They provide critical information about size, shape, and growth patterns, which help guide further diagnostic evaluation. Additionally, serial imaging over time allows for monitoring changes in nodule size and appearance, aiding in the early detection of malignant nodules.

It is well documented that the larger the nodule, the more likely it is to be malignant, and thus, *nodule size* is a major influencing factor in all risk prediction models and nodule management guidelines.[13,14,29–32] In a prespecified analysis using data from the NELSON trial, it was shown that nodules greater than 10 mm in size had a 15.2% probability of malignancy, nodules 5 to 10 mm in

size had a probability of malignancy of 1.3%,[33] while nodules less than 5 mm had a probability of malignancy of 0.04%, suggesting that 10 mm is when malignancy should strongly be considered and diagnostic interventions pursued. Similarly, nodules that demonstrate *growth over time* have been shown to more likely be malignant[32] though benign nodules can also exhibit growth. Volume doubling time (VDT) can be utilized when predicting the probability that a growing nodule is malignant. In the NELSON screening trial, nodules with a VDT of less than 400 days had a 9.9% likelihood of malignancy, nodules with a VDT of 400 to 600 days had a 4% likelihood of being malignant, and nodules with a VDT of greater than 600 had a 0.8% likelihood of being malignant.[34]

Nodule spiculation (**Figs. 4** and **5**) has also been demonstrated in prospective and retrospective studies to be strongly associated with malignancy.[13,14,32,35]

The *location of lung nodules* can provide valuable insights into their nature. Perifissural nodules are highly reassuring indicators of benign processes. This was demonstrated in subset analysis of data from the NELSON trial, where of the 4026 nodules detected, 20% were perifissural, and remarkably, all proved benign on follow-up, even those that had shown growth.[36] A non-LCS trial further corroborated these findings, where about 21% of individuals were found to have perifissural nodules, none of which turned malignant over a median follow-up period of 4.5 years.[37] Such compelling evidence suggests that perifissural nodules are overwhelmingly likely to be benign, potentially eliminating the need for further follow-up imaging.

In contrast, nodules in the upper lobes warrant a more cautious approach. Both prospective and retrospective studies have consistently linked upper lobe nodules to an increased risk of malignancy.[13,14] Consequently, these nodules should be viewed with a higher index of suspicion and may require more vigilant monitoring.

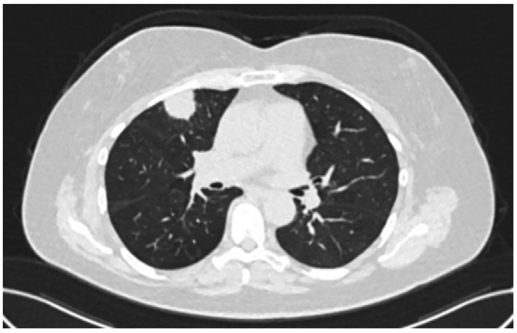

Fig. 4. Right upper lobe nodule, 26 mm, solid and spiculated.

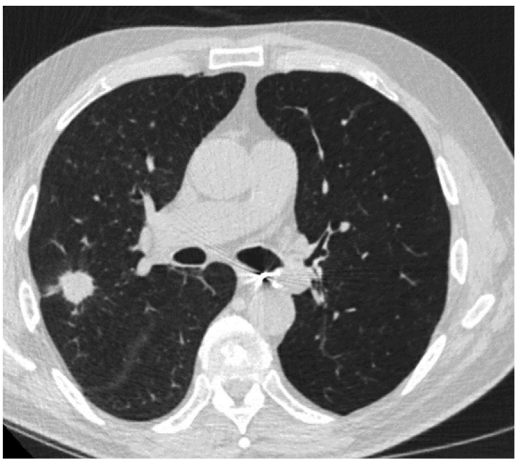

Fig. 5. Right upper lobe, 20 mm solid, spiculated nodule with pleural tenting.

Calcification within a nodule is frequently a sign of benign etiology; however, punctate or eccentric calcification patterns should raise concern for malignancy.[38] Up to 10% of all primary lung cancers demonstrate calcification on imaging, and up to 16% of all resected malignant nodules, both primary lung and metastatic from elsewhere, had calcification on imaging studies.[39,40] Central, diffuse, and lamellar calcification patterns typically reflect a granulomatous process and are, therefore, generally considered a marker of benignity; however, sarcomas, both primary and metastatic to the lung, can sometimes have these “benign” patterns.[39] Rarely, papillary and mucinous adenocarcinomas from elsewhere in the body can also cause calcified nodules in the lungs.[39] Therefore, it is crucial to carefully scrutinize calcified pulmonary nodules when there is a pre-existing diagnosis of cancer.

Fat attenuation is common in hamartomas, benign tumors composed of fat, calcium or bone, cartilage, and connective tissue. Thus, if fat is identified, this is considered a reassuring finding for benignity and suggests a pulmonary hamartoma for which further evaluation can be deferred.[10]

Subsolid nodules, particularly PSNs (see **Fig. 3**), are more likely to be malignant than pure GGNs and solid nodules, even when standardizing for nodule size.[13,41] Furthermore, there is a strong correlation between the size of the solid component on chest CT and the invasive component on pathology[42,43] and overall survival.[44] Therefore, the size of the solid component is essential when making management decisions.

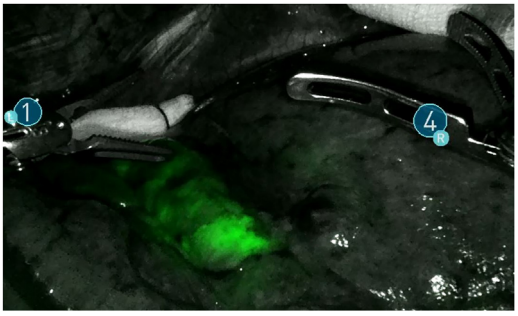

Fig. 6. ICG fiducial (compliments of R. Campagna).

A *pleural tag or tenting*, best seen on CT scans, refers to the inward displacement of the visceral pleura toward a nodule or mass (Fig. 6) and can provide important information about the nodule's characteristics. While the finding of pleural tenting in a lung nodule is not specific to cancer and can be seen with benign conditions, particularly those causing local inflammation or fibrosis, the finding increases the suspicion of malignancy. It should be interpreted as part of a comprehensive assessment of the nodule characteristics and the patient's risk factors. Studies have reported the presence of pleural tenting in pulmonary nodules is associated with an increased likelihood of malignancy and suggests a more invasive or aggressive nature of the nodule.[45]

Radiologic features of nodules and their impact on the likelihood of malignancy are outlined in Boxes 3 and 4.

MALIGNANCY RISK PREDICTION TOOLS

Frequently, patients will have clinical and radiographic characteristics that "conflict," with factors suggesting a nodule is benign and factors suggesting it may be malignant; thus, estimating malignancy and determining the next steps become challenging. Risk calculators incorporate several patient-specific and nodule-specific characteristics outlined earlier that can aid in determining a more concrete probability that a nodule is malignant. The most utilized risk calculators include the Mayo Clinic Model, Brock University Calculator, and the Herder Model, which rely on multivariate logistic regression analysis to generate a percent likelihood of malignancy. The Mayo Clinic Model was derived and validated in patients with solitary lung nodules on chest radiograph.[14] In contrast, the Brock University Calculator was derived and validated in patients with nodules found on LCS scans.[13] The Herder Model is simply the Mayo Clinic Model augmented by PET-CT findings.[46] In a validation study, the Mayo Clinic Model and Brock University Calculator were equally effective in predicting malignancy; however, the Herder Model best predicted the probability of malignancy.[47] The models performed best at predicting malignancy when applied to patients most similar to the subjects in the original derivation cohort used to generate the risk calculator, resulting in an unknown performance of the calculators in populations not included in the cohort studies.

Box 3
Radiographic features associated with a nodule being malignant

- Larger size[13,14,29–32]
- Nodule growth over time[32]
- Spiculation[13,14,32,35]
- Upper lobe location[13,14]
- Punctate or eccentric calcification pattern[38]
- PSN[13,41]
- Pleural tag or tenting[45]

Box 4
Radiographic features associated with a nodule being benign

- Perifissural location[36,37]
- Central, diffuse, or lamellar calcification pattern[39]
- Presence of fat attenuation[10]

CURRENT GUIDELINES

Several professional societies have published guidelines to standardize pulmonary nodule management and assist clinicians in decision-making. The Fleischner Society, American College of Chest Physicians (ACCP), and British Thoracic Society (BTS) provide recommendations based on nodule size and number. The Fleischner Society (updated 2017)[29] and ACCP (updated 2013)[30] guidelines focus on incidentally detected nodules and use nodule diameter measurements.

For solid nodules less than 8 mm, both guidelines are further tailored by recommendations to consider risk factors such as patient age, smoking history, nodule location, and spiculation to categorize patients into high-risk and low-risk groups. For solid nodules greater than 8 mm, the Fleischner Society suggests additional imaging, biopsy, or resection without specific guidance on choosing between options. The ACCP recommends using validated risk prediction calculators to estimate pretest cancer probability, guiding

decisions among further monitoring, biopsy, and resection.[29,30]

The BTS guidelines (updated 2015) apply to incidentally and screen-detected nodules. They emphasize software-derived volumetric assessment for nodule size, which may limit broad application due to technology availability. For solid nodules less than 8 mm or 300 mm^3 or less, BTS does not differentiate follow-up recommendations based on risk factors. However, for larger nodules (>8 mm or $\geq$300 mm^3), BTS aligns with ACCP in advocating the use of risk prediction models (Brock and Herder) to determine the next steps.[31]

For subsolid nodules, the guidelines provide recommendations based on appearance. The Fleischner Society guidelines recommend no further follow-up for a GGN less than 6 mm,[29] while ACCP and BTS guidelines recommend the same with a nodule size cutoff of less than 5 mm.[30,31] All guidelines recommend repeat imaging at varying but similar intervals for larger pure GGNs. Similarly, for PSNs, the Fleischner Society recommends no follow-up imaging for nodules less than 6 mm,[29] and ACCP and BTS have similar recommendations for nodules less than 8 mm and less than 5 mm, respectively. For large PSNs, all guidelines recommend repeat imaging at varying but similar intervals.[30,31] **Tables 1** and **2** summarize the 3 major guidelines for the follow-up of solid and subsolid solitary nodules.

IMAGING MODALITIES FOR LUNG NODULES

Detecting and monitoring lung nodules can be achieved with various imaging modalities, including chest radiography (CXR), CT, PET-CT, and MRI. CXR, though easy to obtain and relatively inexpensive, has not been shown to detect nodules reliably. A Prostate, Lung, Colorectal, and Ovarian randomized screening trial investigated whether annual CXRs over 4 years in 154,901 participants reduced lung cancer mortality and found no benefit during a 13 year follow-up period.[48] Similarly, the NLST compared low-dose CT (LDCT) versus CXR annually for 3 years in 53,454 participants and found a 20% relative reduction in lung cancer mortality among those randomized to LDCT.[8] It is felt that CXR is not sensitive enough to detect nodules due to the number of overlapping structures and low contrast of nodules on radiography.[49]

Chest CT is the preferred method of nodule detection and monitoring because it allows for more precise measurement of nodule size initially and over time, can identify the presence of calcification or fat, identify spiculation, reveal proximity to a fissure as well as assess for regional adenopathy. It is, therefore, the recommended imaging test in all guidelines for nodule detection and monitoring.

PET-CT using 18F-fluorodeoxyglucose (FDG) is a functional imaging modality routinely employed to further risk stratify lung nodules. PET-CT is incorporated as an adjunctive test in all current nodule management guidelines once a nodule is greater than 8 mm in size and there is a moderate-to-high probability that a nodule is malignant. Importantly, to avoid false-negative results, PET-CT should neither be utilized for solid nodules less than 8 mm in size due to the spatial resolution limitations nor be utilized for pure GGN or subsolid nodules where the solid component is less than 8 mm as these can be well-differentiated carcinomas with mild atypia that have low FDG-uptake.[50,51] While a lack of FDG uptake does not exclude the possibility of cancer or obviate serial monitoring via CT, it does make malignancy less likely and allows for a less-invasive management approach.[51] It is generally accepted that a standardized uptake value (SUV) of 2.5 is considered "positive" and should prompt additional workup, typically in the form of biopsy or resection.[51] However, it is important to recognize that SUV can be underestimated in smaller nodules (<10 mm) due to partial volume effect and for nodules near the diaphragm due to respiratory motion.[51] In addition, the potential for false-positive results when a nodule is due to infection, radiation fibrosis, rheumatoid arthritis, cryptogenic organizing pneumonia, or sarcoid, for example.[50] Hence, though PET-CT scans are informative, they are only one of many pieces of information that a clinician should use to determine the best management strategy for a lung nodule.

Lastly, *MRI* has become an area of interest as a potential alternative to CT scans because of the lack of exposure to ionizing radiation. A prospective multicenter study of 567 participants with or at risk for COPD underwent contrast-enhanced MRIs where nodule size, morphologic features, and Lung Imaging Reporting and Data System (Lung-RADS) categories were assessed by 2 blinded radiologists and compared to same-day LDCT as the reference standard.[52] Of the 525 nodules found on LDCT, reader 1 identified 316 of 525 (60.2%), and reader 2 identified 302 of 525 (57.5%) on MRI. MRI was noted to have low sensitivity for solid nodules less than 6 mm in size, similar to results found in smaller single-center studies,[53,54] but had a sensitivity of 73.3% and 71.4% for readers 1 and 2, respectively, for solid nodules greater than 6 mm in size. Notably, sensitivity for part solid and GGNs was low, 5%, regardless of size; however, this may have been due to the low incidence of such nodules in the patients sampled

Table 1
Guideline comparison for solid lung nodule

Guidelines	Small	Intermediate	Large	Notes
Fleischner Society 2017[29]	*<6 mm* *Low risk*: no follow-up CT imaging *High risk*: optional 1 y follow-up CT decision informed by number of patient risk factors	*6–8 mm* *Low risk*: CT at 6–12 mo, consider CT at 18–24 mo *High risk*: CT at 6–12 mo, then repeat CT at 18–24 mo	*>8 mm* *Low and high risk*: Consider CT at 3 mo, PET/CT or tissue sampling or resection	Low risk: young age, less smoking, regular margins, not in upper lobe High-risk factors = older age, heavy smoking, spiculated, upper lobe location Not applicable in patients aged <35 y, history of cancer, immune compromised
ACCP 2013[30]	*≤4 mm* *Low risk*: no follow-up CT imaging *High risk*: repeat CT in 1 y *5–6 mm* *Low risk*: repeat CT 1 y *High risk*: repeat CT 6–12 mo, then repeat CT 18–24 mo	*6–8 mm* *Low risk*: CT at 6–12 mo, then repeat CT at 18–24 mo *High risk*: CT at 3–6 mo with repeat at 9–12 mo and again at 24 mo	*>8 mm* Estimate probability of malignancy using clinical judgment or validated prediction model Probability of malignancy <5%, recommend serial CT scans at 3, 6, 9–12, and 18–24 mo Probability of malignancy 5%–65%, recommend PET-CT Probability of malignancy <40% and PET-CT is negative, recommend serial CT scans at 3, 6, 9–12, and 18–24 mo Probability of malignancy 10%–60%, recommend nonsurgical biopsy Probability of malignancy >65% or if the nodule is intensely hypermetabolic on PET-CT, recommend resection	Low risk (<5%): young age, less smoking, regular margins, not in upper lobe Intermediate risk: (5%–65%): mixture of high-risk and low-risk features High risk (>65%): older age, heavy smoking, prior cancer, spiculated, upper lobe location

(*continued on next page*)

Table 1
(*continued*)

Guidelines	Small	Intermediate	Large	Notes
BTS 2015[31]	*<5 mm or <80 mm³* no follow-up CT imaging	≥5 mm to 8 mm or >80 mm³ to <300 mm³ *≥5–6 mm:* calculate VDT with repeat CT at 1 y If stable on basis of volumetric measurement, no further imaging needed If VDT <400 pursue further workup and consider definitive management • If VDT 400–600 d consider biopsy, or further CT surveillance depending on patient preference • If VDT is >600 d consider discharge or ongoing CT surveillance per patient preference • If stable on 2 dimensional diameter measurements used to assess growth for 2 y can discharge >6 mm or ≥80 mm³: Calculate VDT with repeat CT at 3 mo • If nodule grows with VDT <400 d pursue further workup and consider definitive management • If VDT>400 repeat CT 1 y from baseline and follow recommendations for nodules ≤5–6 mm moving forward	*>8 mm or ≥300 mm³* Estimate pretest probability of cancer with Brock model if >50 y old with tobacco history Consider estimating pretest probability with the Brock model in all patients regardless of age or tobacco history Pretest probability <10% assess growth rate on interval scans Pretest probability >10% with Brock model, recommend PET-CT scan and then reassess risk after PET-CT using Herder Prediction model Risk of malignancy <10%, consider CT surveillance Risk of malignancy 10%–70%, consider biopsy, Excisional biopsy or CT surveillance per patient preference Risk of malignancy >70%, recommend resection	VDT of >25% is considered significant growth Not applicable in patients aged <18 y

Table 2
Guideline comparison for subsolid lung nodule

Guidelines	Small Pure GGO	Large Pure GGO	Small Part Solid	Large Part Solid
Fleischner Society 2017[29]	*<6 mm*: no follow-up CT imaging	*>6 mm*: CT at 6–12 mo then every 2 to 5 y total if stable	*<6 mm*: no follow-up CT imaging	*>6 mm*: CT at 3–6 mo followed by annual screening to 5 y if stable
ACCP[30]	*<5 mm*: no follow-up CT imaging	*>5 mm:* annual CT for at least 3 y if stable *if >10 mm earlier follow-up at 3 mo may be indicated	*<8 mm*: follow-up CT at 3, 12, and 24 mo followed by annual CT for 1–3 y if stable	*>8 mm:* follow-up CT at 3 mo followed by PET, nonsurgical biopsy, or resection PET only if solid component >8 mm If >15 mm, should proceed directly to PET, nonsurgical biopsy, or resection
BTS[31]	*<5 mm*: no follow-up CT imaging	*>5 mm*: CT at 3 mo if persists and stable assess risk with Brock model. If <10% risk malignancy, repeat CT at 1, 2, and 4 y if stable If risk malignancy >10%, repeat CT at 1, 2, and 4 y or biopsy or resection depending on patient preference	*<5 mm:* no follow-up CT imaging	*>5 mm:* CT at 3 mo if persists and stable, assess risk with Brock model. If <10% risk malignancy, repeat CT at 1, 2, and 4 y if stable If risk malignancy >10%, repeat CT at 1, 2, and 4 y or biopsy or resection depending on patient preference

in the study and not indicative of a shortcoming of the MRI modality.[52] In addition, radiologists systematically underestimated long-axis and short-axis diameter measurements on MRI compared to LDCT measurements within 1 mm, which influenced Lung-RADS categorizations, such as misclassifying a category 3 as a category 2, resulting in a 12 month instead of a 6 month follow-up imaging.[52] Compared to LDCT, MRI had a low sensitivity for detecting morphologic features such as spiculation 41% and 66% sensitivity for readers 1 and 2, respectively, cavitation 66.7% and 77.8% sensitivity for readers 1 and 2, respectively, bronchial cutoff sign 41.7% sensitivity for both readers. Both readers failed to detect nodule calcification in 14 of 14 calcified nodules. The inability to recognize calcification, typically a marker of benignity, led to unnecessary follow-up for calcified nodules. Furthermore, lack of recognition of nodule spiculation, a marker of malignancy, led to Lung-RADS category 4X being under-called on MRI. Studies have indicated that using ultrashort echo time MRI may improve MRI sensitivity for morphologic features such as calcification and spiculation.[52] Also concerning was lack of MRI sensitivity for cavitation and bronchial cutoff signs, both indicators of malignancy compared to CT. Due to the shortcomings mentioned earlier compared to LDCT, MRI is not routinely recommended at this time.[52]

BIOMARKERS

Pulmonary nodules that fall in the broad intermediate risk category (5%–65%) require a tissue diagnosis if accompanied by a suspicious PET scan.[30] Progress in noninvasive testing to further risk stratify lung nodules to avoid unnecessary invasive testing shows promise. The biomarker field is rapidly evolving (reviewed elsewhere[55,56]), with several products on the market (**Table 3**).[57–62] Biomarker tests are not widely incorporated in nodule management algorithms, lacking data from randomized controlled trials on improved patient outcomes or cost-effectiveness.[56]

As one example, the pulmonary nodule plasma proteomic classifier (PANOPTIC) trial assessed the integrated classifier Nodify-XL2, a test combining assays for 2 proteins, with age, smoking status, nodule diameter, edge characteristics, and location to yield a posttest probability of benign versus malignant. The study included 178 patients with 8 to 30 mm nodules and a pretest probability of cancer of 50% or less.[59] Results demonstrated a sensitivity of 97%, a specificity of 44%, and a negative predictive value of 98% for cancer.[59] These results were reported after 1 year but remained accurate at 2 years of follow-up.[63] Extrapolating this finding, applying the integrated classifier to patient care would yield 40% fewer procedures on benign nodules, and 3% of malignant nodules would be misclassified.[59] Validation trials of biomarkers will help determine how to deploy these evolving tools.

DIAGNOSTIC MODALITIES

The decision on how to sample a nodule hinges on the clinical scenario, institutional expertise, and a discussion of the risks and benefits of different sampling modalities. CT-guided biopsy may be appropriate for a peripheral, solitary nodule less than 3 cm in a patient without emphysema, while a bronchoscopic approach may be favored in the presence of emphysema or if guidelines necessitate simultaneous sampling of nodes.[64]

Knowing the anticipated diagnostic yield and risk of biopsy modalities frames patient counseling. However, heterogeneity in the definition of diagnostic outcomes complicates the interpretation of studies assessing the diagnosis of pulmonary nodules.[65,66] The 2015 Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines aim to prevent such discrepancies by providing a 30 item checklist that can be referenced when designing and interpreting studies.[67] The 2015 STARD checklist can be found at http://www.equator-network.org/reporting-guidelines/stard.

Computed Tomography-guided Biopsy

CT-guided biopsy offers real-time imaging of the needle entering the lesion and has high sensitivity and specificity (**Table 4**).[68–70] Trade-offs include a false-negative rate of approximately 16%[71] and a pneumothorax (PTX) rate of 25.9%, with 6.9% of biopsies requiring a chest tube.[72] Diagnostic accuracy falls off with nodules 1 cm or less and a greater needle path length (>4 cm).[73] Some factors that increased the PTX rate included crossing a fissure or bulla, the presence of emphysema, a lesion less than 4 cm or without pleural contact, and lesions 3 cm or deeper from the pleural surface.[72] Some techniques such as normal saline tract sealant reduce the chest tube rate to less than 1% in some circumstances,[74] but clinicians should know their institutional outcomes for counseling patients.

Fiberoptic Bronchoscopy

Biopsying a nodule by bronchoscopy does not necessitate crossing the pleura and comes with a lower PTX risk. Unguided or fluoroscopic-

Table 3
Biomarker studies under development

Test Name	Company	Biomarker Assay Type	Population	Data
LCP CNN[57] (Lung Cancer Prediction Convolutional Neural Network)	Optellum (Oxford, UK)	Deep learning algorithm applied to chest CT	Trained on NLST dataset (currently smoking or formerly smoked, 55–75 y old, ≥30 pack-years)	AUC better than Brock and Mayo models, 83.5%–91.9%
Lung EpiCheck[58]	Nucleix (San Diego, CA, USA; Rehovot, Israel)	Six-marker panel methylation-based plasma test	Age ≥ 50 y Tobacco history	AUC 0.88–0.90 *LCO* (sens/spec)*:* 76.7%–87.2%/64.2%–93.3% *HCO* (sens/spec)*:* 56.7%–74.3%/90%–100%
Nodify-XL2[59]	Biodesix (Boulder, CO, USA)	Proteomic analysis of plasma proteins LG3BP and C163 A	≥40 y old nodule 8–30 mm	Sens 97% Spec 44% NPV 98%
Nodify-CDT[60]	Biodesix (Boulder, CO, USA)	Seven autoantibodies to tumor-associated antigens (p53, NY-ESO-1, CAGE, GBU4-5, SOX2, HuD, and MAGE A4)	Age 50–75 y, tobacco history	Spec 90.4% Sens 32.1%
Precepta[61]	Veracyte (South San Francisco, CA, USA)	Whole-transcriptome RNA sequencing of nasal brushings	Tobacco ≥ 100 cigs, nodule ≤ 30 mm	*Low risk:* Sens 97% Spec 40% *High risk:* Sens 57% Spec 92%
REVEAL[62]	MagArray (Milpitas, CA)	Magnetic nanosensor detection of 3 proteins: epidermal growth factor receptors, prosurfactant protein B, and tissue inhibitor of metalloproteinases 1	Tobacco use, nodule 4–30 mm	Sens 94%, NPV 94%

Table 4
Nodule biopsy modalities and associated diagnostic yield and complications

Technique	Yield	Complications	References
CT-guided biopsy	93% yield 92% if <2 cm 52% if <10 mm ~20% nondiagnostic	PTX: 25.9% Chest tube: 6.9% Pulmonary Hemorrhage: 7.1%–16%	68–70,72,73
Standard bronchoscopy	36%–88% sensitivity 63% if >2 cm 34% ≤ 2 cm	PTX: 2%–4% Bleeding: 2%–5%	75
Standard bronch + rEBUS	70.9% (67.9%–73.9% CI) 50%–66% if 1–2 cm	PTX: 2.9%	69,76,91
Thin bronch + EBUS *UltraThin (UT) bronch* *Thin bronch/UT + CBCT*	62.6% (55.3%–70.0% CI) 50.2% (37.3%–63.2% CI)	PTX: 1.1% both Total complications 2.8% (UTB) vs 4.5% (TB)	77,78,91,94
ENB *ENB with tomosynthesis*	70.3% 77.4%–87% 75% if <2 cm	PTX: 3.4%, with 1.7% with tube PTX: 1.8%–2.6%	79,81,82,84,92
Robotic bronchoscopy	77.6% (70.4%–84.8% CI)	PTX: 1.5%–2.7%, with 1.2%–1.5% with tube Hemorrhage: 0.5%	79,82,88,91
Robotic bronchoscopy + image assistance	78.3%–93.3%	PTX: 2.0%–3.3%	86,88,95

Abbreviations: CBCT, cone beam CT scan; ENB, electromagnetic navigational bronchoscopy; PTX, pneumothorax; rEBUS, radial endobronchial ultrasound; UT, ultrathin.

assisted standard bronchoscopy performs better for nodules over 2 cm (63% vs 34% sensitivity), but the yield remains highly variable.[75] The addition of radial endobronchial ultrasound (rEBUS) to unenhanced fiberoptic bronchoscopy results in higher yields, though still lower than transthoracic needle aspiration (TTNA). One meta-analysis reported a yield of 83.5% for TTNA versus 68.8% for rEBUS-directed bronchoscopy (rEBUS-TBB). TTNA yield remained stable for 1 to 2 cm lesions at 83%, while rEBUS-TBB dropped to 50%, though rEBUS-TBB had a significantly lower risk of PTX (2.9% vs 21.4%).[76]

Thin and Ultrathin Bronchoscopy

Both thin (~4 mm external diameter) and ultrathin (≤ 3.5 mm external diameter) bronchoscopes enable the operator to navigate the bronchoscope further into the lung, as far as fifth-generation airways for ultrathin bronchoscopes. Ultrathin bronchoscopes have a higher yield than thin bronchoscopes, 70.1% versus 58.7%, respectively, partly due to the deeper navigation.[77] Ultrathin scopes with a 1.7 mm working channel provided a higher yield than those with a 1.2 mm channel (70% vs 61%, respectively), likely due to rEBUS capability.[78] Higher yields occur for nodules with a bronchus sign (72% vs 47%) and nodules greater than 2 cm (80% vs 53%).[78]

Electromagnetic Navigational Bronchoscopy

Electromagnetic navigational bronchoscopy (ENB) uses a planning CT scan and sensors to guide a 2.7 mm catheter to the target nodule. Earlier versions of ENB, at most assisted by rEBUS and fluoroscopy, provide a yield of 70.3% but with a range across studies from 26.7% to 96.8%,[79] likely reflecting case selection and operator experience. CT-to-body divergence remains a well-recognized limitation for ENB and robotic-assisted bronchoscopy (RAB) and refers to anatomic differences in the preprocedure CT scan, usually done with a breath hold, and the lung at the time of the procedure.[80] Newer versions of ENB address this divergence by pairing with tomosynthesis, increasing the yield to 79% to 87% with similar complication rates to ENB without tomosynthesis.[81–84] The randomized controlled (navigation endoscopy to reach indeterminate lung nodules versus transthoracic needle aspiration [VERITAS]) trial compared ENB with tomosynthesis to CT-guided biopsy and found the same diagnostic yield for the 2 approaches (76%), though with nearly a 6 fold higher complication rate with CT-guided biopsy.[85] Cone beam CT (CBCT) also addresses divergence and

leads to similar yields, 71% to 87%, depending on the study.[86]

Robotic-assisted Bronchoscopy

A drawback of ENB is catheter movement with tool insertion.[87] RAB offers a more stable platform for nodule biopsy with the potential for higher yields. RAB combined with 2 dimensional fluoroscopy and rEBUS provides improved yields over earlier versions of ENB, from 77% to 81.8%.[82,88] Robotic bronchoscopy paired with CBCT provided a yield of 78.4%[89] to 93.3%,[88,90] with one study noting an impact of a bronchus sign (89.9% with, 80.2% without).[86]

Impact of Confirmatory Imaging

A pulmonary nodule may be definitively targeted if it is visible endobronchially or abuts an airway amenable to linear ultrasound location. Otherwise, nodule location can remain uncertain even with ENB or RAB, given CT to body divergence from respiratory variation and procedural atelectasis. A meta-analysis demonstrated no significant difference in yield from guided bronchoscopy before 2012 compared to 2012 to 2021 (70.5% vs 69.2%, $P > .05$).[91] The timeframe of the meta-analysis precedes more recent studies on the potential benefit of augmented radiology in providing an updated tool in lesion information to optimize localization. As alluded to in previous sections, the current technologies include digital tomosynthesis (DT) with augmented fluoroscopy and CBCT. DT uses multiple radiographic images to reconstruct a more 3 dimensional image of tool–target relationship. Versions of DT are found in Medtronic Illumisite, Noah Medical Galaxy, and LungVision (Body Vision Medical Ltd, Ramat Ha Sharon, Israel). Currently, limited data are available for the Noah and LungVision systems. The use of DT with ENB (Illumisite) resulted in a 25% higher yield than conventional ENB for one group (79% vs 54%).[83] Others have found 7% to 13% higher yields pairing ENB with DT compared to their prior ENB yields.[81,92]

CBCTs can be fixed or mobile; in contrast to a standard CT, the CBCT rotates around a fixed region of the patient to obtain images. The impact of CBCT can be significant, such as with thin/ultrathin bronchoscopy, where it increases navigational success by 20% to 30%[93] and diagnostic yield by 25%.[94] However, one multicentered study of shape-sensing RAB showed no difference in yield with or without CBCT.[95] Of note, procedures using CBCT averaged 30 minutes longer with significantly more radiation exposure ($\sim$1000 $\mu Gy/m^2$).[95] Comparison of radiation doses from CBCT versus percutaneous biopsy approaches proves challenging given different imaging modalities for percutaneous approach, but radiation doses appear similar based on available data.[86]

Tool Selection

Navigational technologies paired with CBCT or DT can markedly improve navigation to a nodule, but biopsy yield lags behind navigation success.[93] Some of the sampling shortcomings stem from tool limitations. Studies have found that the more tools used, the higher the diagnostic yield. An example study using ENB, cytology brush, and forceps made a diagnosis approximately 50% of the time, with 43% of the yield being from the needle biopsy. Combining all sampling modalities increased the final yield to 69%.[96] In a small study pairing cryobiopsy, standard biopsy tools, and ENB with tomosynthesis, one group obtained a diagnostic yield of 93%, with yield by tool being TBNA at 69%, forceps at 60%, and 1.1 mm cryoprobe at biopsy at 60%.[97] Comparing forceps to the Medtronic GenCut core biopsy, 78.2% of positive sampling stemmed from forceps. In comparison, Gencut was positive 73.6% of the time, with only GenCut being positive 14.6% of the time,[98] again demonstrating an additive effect utilizing multiple tools.

Table 5
Characteristics of bronchoscopy tools

Sampling Modality	Frequency Tool Made Diagnosis[93,96,97,99]	Representative Tool Cost
Wash/bronchoalveolar lavage	31%–43%	N/A
Brush	39.9%–74%	US$25
Transbronchial needle aspiration/TBNA	43%–69%	US$175
GenCut	58.7%	US$435
Forceps	60%–92%	US$50
Cryoprobe 1.1 mm	60%–90%	US$500

Representative cost is the purchase price of similar tools at authors' institution.

Similar benefits have been reported with RAB. In one study, sequential biopsies of nodules averaging 21 mm with a 21g needle, followed by 1.8 mm forceps, followed by cryobiopsy with a 1.1 mm probe found that each tool added to the overall yield; cryobiopsy was diagnostic in 76.9% of cases versus 42.3% for the needle and 57.7% for forceps.[99] Importantly, in the Clinical Evaluation of superDimension Navigation System for Electromagnetic Brochsocpy or NAVIGATE trial, using more tools did not increase the rate of PTX or procedural bleeding.[100] Rapid onsite cytologic examination (ROSE) decreases the number of needle passes in EBUS lymph node biopsy without impacting diagnostic yield.[101] However, whether ROSE combined with touch imprint cytology would limit the total number tools in RAB or ENB is unknown. Drawbacks of sampling with numerous tools include the additional procedural time and the added cost of additional tools. **Table 5** shows the value of different tools when a diagnosis is made.

Surgical Approaches

Patients with intermediate-risk or high-risk nodules based on risk assessment, including findings on CT-PET that show no suspicion of hilar or mediastinal nodes necessitating preoperative nodal staging, should be considered for surgical resection.[30] A minimally invasive surgical approach is preferred; the transition from open surgical procedures to a video-assisted thoracoscopic approach has lowered the surgical mortality rate from 3% to 8% to 2% to 3% and severe complication rate from 7% to 38% to 0% to 18%, respectively.[102]

GGNs and small nodules may not be visible or palpable to permit localization during resection. Meta-analyses have demonstrated the safety and efficacy of marking nodules to assist with surgical resection, with a 0.97 (95% confidence interval [CI] 0.95–0.99) success rate.[103–105] A bronchoscopic approach enables marking of multiple nodules if necessary, without increased PTX risk. For single lesions, using bronchoscopy to mark with indocyanine green (ICG) had a similar success rate to CT-guided marking (98.3% vs 94.3%), with a lower complication rate.[105] Embolization coils soaked in ICG can be placed even 9 to 14 days before resection[106] (see **Fig. 6**) with continued fluorescence with the Firefly imaging system from the da Vinci robotic platform.

SUMMARY

Pulmonary nodule management hinges on appropriate risk stratification, which, to date, has relied on patient and imaging characteristics. Biomarker testing likely improves risk stratification, while radiographic confirmation and tool options may boost bronchoscopic diagnostic yields. Together, these advances should improve the diagnosis of early stage lung cancer while limiting unnecessary invasive testing for benign lesions.

CLINICS CARE POINTS

- Increasing numbers of pulmonary nodules are detected annually, and the vast majority is benign.
- Risk prediction models help assess the probability of malignancy. Biomarker validation studies are underway that may improve risk assessment.
- Multiple societies have published guidelines for pulmonary nodule management.
- Regardless of the modality used, the bronchoscopic yield for nodule sampling has been approximately 70% for the last 2 decades. However, pairing navigational technologies with radiographic confirmation of tool-in-lesion and deploying multiple tools appears poised to boost yields.

DISCLOSURE

None.

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