Lung nodules: A comprehensive review on current approach and management

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Abstract:

In daily clinical practice, radiologists and pulmonologists are faced with incidental radiographic findings of pulmonary nodules. Deciding how to manage these findings is very important as many of them may be benign and require no further action, but others may represent early disease and importantly early-stage lung cancer and require prompt diagnosis and definitive treatment. As the diagnosis of pulmonary nodules includes invasive procedures which can be relatively minimal, such as bronchoscopy or transthoracic aspiration or biopsy, but also more invasive procedures such as thoracic surgical biopsies, and as these procedures are linked to anxiety and to cost, it is important to have clearly defined algorithms for the description, management, and follow-up of these nodules. Clear algorithms for the imaging protocols and the management of positive findings should also exist in lung cancer screening programs, which are already established in the USA and which will hopefully be established worldwide. This article reviews current knowledge on nodule definition, diagnostic evaluation, and management based on literature data and mainly recent guidelines.

Keywords:
Low-dose computed tomography, lung cancer screening, lung nodule management, lung nodules

The incidental finding of lung nodule(s) in asymptomatic individuals is an increasingly common clinical dilemma encountered by radiologists and pulmonologists in daily clinical practice. Accurate identification and characterization of malignant lung nodules and development of clear algorithms for their management, permitting cure of early-stage lung cancer while avoiding morbidity, patient distress and increased costs caused by more invasive and unwarranted for benign disease approaches, remain a challenge.

Several scientific societies, including the Fleischner Society,[1] the British Thoracic Society (BTS),[2] the American College of Chest Physicians (ACCP),[3] and the National Comprehensive Cancer Network,[4] have published guidelines recommending algorithms for the management of lung nodules. Despite rather minor discrepancies, all proposed approaches take into consideration clinical risk factors for lung cancer, nodules imaging features, and previous imaging studies to assess the probability of malignancy and the most appropriate management. However, most of these recommendations are rather weak, relying on low-quality evidence, and current guidelines are only followed by a minority of clinicians (approximately 40%).[5] Moreover, the management of most patients presenting with incidental lung nodule(s) seems to rely largely on clinical judgment although evidence suggests that clear algorithms and a multidisciplinary approach are required.

Nodule management will become even more important, as evidence from the landmark National Lung Screening Trial (NLST) study, but also from the recently presented but yet unpublished NELSON trial, suggests that screening with low-dose computed tomography (CT) in high-risk individuals

may reduce lung cancer mortality through the timely identification of malignant nodules corresponding to early-stage disease.[6]

The aim of this article is to provide a comprehensive review of the current knowledge on lung nodules and an accurate approach of their management based on all currently available guideline recommendations.

What is Described as a Pulmonary Nodule?

According to the glossary of terms for chest imaging proposed by the Fleischner Society, a lung nodule is defined as an approximately rounded opacity more or less well-defined measuring up to 3 cm in diameter.[7] Rounded lesions measuring more than 3 cm in diameter are termed lung masses and should be considered indicative of lung cancer until histologically proven otherwise. Lung mass approach differs from that of nodules and will not be further discussed in this article.

Depending on their attenuation in CT imaging, lung nodules are categorized in three different types: (i) solid nodules, the most common type, characterized by homogeneous soft-tissue attenuation, (ii) ground-glass nodules, nonuniform in appearance with a hazy increase in local attenuation of lung parenchyma not obscuring the underlying bronchial and vascular structures, and (iii) part-solid nodules, comprising both solid and ground-glass attenuation components.

Lung nodules may be solitary or multiple. To be considered solitary, a nodule must be completely surrounded by normal lung parenchyma, without associated atelectasis, enlargement of the hilum, or pleural effusion.[3,8] In contrast to the general impression, many individuals are found with multiple nodular lesions, especially nonsolid nodules. In the NELSON trial, only approximately half of the individuals screened presented a solitary pulmonary nodule,[9] while in two other screening cohorts, the median nodule count at baseline was 5 and 7, respectively.[10] In line with the NELSON trial management algorithm,[11] an approach to multiple nodules based on the larger or more suspicious nodule is generally proposed,[1,2] but separate evaluation of each nodule without *a priori* denying curative intent therapies has also been recommended,[3] as many studies have shown that patients with malignant dominant nodules present benign satellite lesions.[12-14] It should be noted that the larger of multiple nodules is not always the malignant one. In the PanCan screening cohort, in approximately 20% of patients diagnosed with lung cancer, the malignant nodule proved not to be the largest one (in one case, it was actually only the fifth largest).[10]

The differential diagnosis of lung nodules is broad [Table 1]. The occurrence of relevant symptoms, the number of nodules, and their particular imaging characteristics (location, shape, presence and type of calcifications, and presence of spiculation or cavitation) may substantially narrow the differential diagnosis or even point toward a specific entity.

How Often are Lung Nodules Encountered?

In previous reports, nodule detection in the US was approximately 150,000 per year.[8,15] This estimate was largely based on historical data from studies using

Table 1: Lung nodules differential diagnosis

Neoplasms
  Malignant
    Bronchogenic lung cancer
    Lymphoma
    Carcinoid
    Sarcoma
    Lung metastases
  Benign
    Hamartoma
    Chondroma
    Lipoma
    Respiratory papillomatosis
    Pulmonary benign metastasizing leiomyoma
Infections
  Mycobacteria
  Fungi
  Round pneumonia
  Lung abscess
  Septic emboli
  Nocardia spp.
  Hydatid cyst
  Q fever
Immune-mediated diseases
  Rheumatoid arthritis
  Granulomatosis with polyangiitis
  Nodular sarcoidosis
  Organizing pneumonia (cryptogenic or secondary)
  Lymphoid granulomatosis
  Necrotizing sarcoid granulomatosis
Congenital abnormalities
  Arteriovenous malformation
  Bronchogenic cyst
  Pulmonary sequestration
  Pulmonary venous varix
  Bronchial atresia with bronchocele
Miscellaneous
  Round atelectasis
  Endoparenchymal lymph node
  Progressive mass fibrosis
  Inflammatory pseudotumor
  Amyloidosis
  Lipoid pneumonia

chest X-ray (CXR) for the detection of nodules showing that a solitary lung nodule was found in 0.09%–0.20% of all CXRs performed at that time.[16,17] Naturally, with the advent of chest CT imaging in daily clinical practice, the incidence of lung nodules has soared. A large retrospective study reported an increase in the annual rate of nodule detection by chest CT from 3.9 to 6.6/1000 person-years in the US between 2006 and 2012.[18] Interestingly, however, the rate of lung cancer diagnosis (63,000 new diagnoses) did not parallel this huge increase in nodule identification. A lower incidence (up to 12.6/100,000 person-years) was found in a similar epidemiological study undertaken in the French general population between 2002 and 2005.[19]

Assessing the Pretest Probability of Malignancy

Assessing the pretest probability of malignancy is the first necessary step in the evaluation of every patient with newly identified lung nodule(s), and this is primarily dependent on the presence or absence of relevant risk factors in the history of individual patients. These risk factors are the following:

Current or past history of tobacco smoking
Tobacco smoking is by far the major risk factor for lung cancer and is implicated in 85% of all cancer-related deaths.[20] The relationship between smoking and lung cancer risk has long been shown to be dose dependent.[21,22] The risk increases with the amount of tobacco consumed daily and more importantly the duration of active smoking.[23] However, there is no threshold below which tobacco smoking can be considered harmless. Smoking cessation diminishes the risk for lung cancer development,[24-26] but even in former smokers, the likelihood of lung cancer occurrence remains higher compared to never smokers.[27,28]

Although most epidemiological data focus on active cigarette smoking, there is also evidence supporting a significant but less strong causal link of other products, such as pipes and cigars,[29-31] as well as second-hand smoking,[32-34] with lung cancer. The introduction of electronic cigarettes has led to a changing landscape in smoking habits, especially in younger populations. Potential harms associated with electronic cigarettes, including carcinogenicity, remain largely unknown, and epidemiologic studies addressing these issues will not be available in the short term. However, there are already experimental data showing that electronic cigarette use is associated with exposure to well-known lung carcinogens[35,36] and may cause DNA damage *in vitro* and *in vivo*.[35,37]

Aging
Older age has been consistently shown to correlate with an increased probability of malignancy in patients with lung nodules and is, in fact, incorporated in all composite prediction models developed for risk assessment in such patients.[10,38-40] More than half of all cancers, including lung cancer, develop above the age of 70.[41,42]

Occupational exposure to carcinogenic agents
Occupational exposure is an often overlooked risk factor for lung cancer. A detailed history of present and past occupations must be an integral part of the initial evaluation of any patient with lung nodules. Several dusts, metals and fumes have been causally linked with lung cancer [Table 2].[43-53] Simultaneous exposure to cigarette smoke acts synergistically, further augmenting lung cancer risk.[54-57] For instance, in nonsmokers with asbestos exposure, the relative risk for lung cancer development is almost twice as high as in unexposed individuals. In smokers, the respective risk is approximately nine times higher.[54]

History of previous lung cancer
Lung cancer survivors are at increased risk for a second primary lung cancer.[58-61] In a study of patients with NSCLC Stage I who underwent surgical resection, the incidence of a second lung cancer was almost seven times higher than that of initial lung cancer in the 1st year following resection and remained four times higher at 10 years.[60]

Patients with head-and-neck squamous cell carcinoma[62,63] or other smoking-related malignant neoplasms, such as bladder or pancreatic cancer,[64,65] are also at increased risk for a synchronous or metachronous primary lung cancer. Furthermore, lung cancer is the second most prevalent solid tumor presenting in Hodgkin disease survivors[66,67] and is also common in non-Hodgkin lymphoma survivors.[68] Radiotherapy and chemotherapy with alkylating agents for index lymphoma treatment have been causally implicated in lung cancer development, both independently and additively.[67-69]

Table 2: Lung carcinogenetic occupational agents

Asbestos[43]
Silica[44]
Soot[45]
Beryllium[46]
Chromium[47]
Arsenic[48]
Nickel[49]
Cadmium[50]
Radon[51]
Diesel fumes[52,53]

Family history of lung cancer

Family history is equally important. Individuals with a family history of lung cancer among first-degree relatives have been consistently shown to have a two-fold higher risk of developing lung cancer themselves.[70,71] Those with multiple affected family members diagnosed at younger age appear to be at greater risk.

Comorbid chronic lung disease

Several studies[72-75] support a strong and independent relationship between chronic obstructive pulmonary disease and lung cancer, extending beyond the common underlying etiology of smoking.[76-78] In the NLST, participants with spirometric evidence of COPD had a two-fold higher lung cancer risk compared to those with normal lung function.[79] Moreover, the presence of emphysema in chest CT scans has been independently correlated with increased lung cancer risk, even after adjusting for airflow limitation.[72]

Lung cancer has also been adopted as a major comorbidity of idiopathic pulmonary fibrosis,[80] with an estimated prevalence of about 10% in this patient group.[81] Although smoking represents a common risk factor for both entities, it has been hypothesized that pulmonary fibrosis *per se* promotes carcinogenesis through so far unclear mechanisms.[81-83]

Comorbid lung diseases as well as consequent functional compromise frequently pose intractable challenges in lung nodule management and should be carefully assessed upon decision-making.

Assessing the Imaging Features of the Nodules

Radiological evaluation is the second step in the approach of patients with lung nodules. Nodule size followed by growth rate is cardinal parameters for lung cancer probability estimation and management decision-making. Other imaging characteristics have also been identified as predictors of a malignant or benign etiology.[2]

Nodule size

Strongly associated with the probability of malignancy, nodule size represents a cornerstone in nodule assessment in all recommended algorithms.[1-4] Based on observations in high-risk patients from lung cancer screening trials,[10,84] a cut diameter below 6 mm is proposed by most recent guidelines as an indicator of acceptably low cancer risk (<1%).[1,4] The same cutoff applies for both solitary and multiple solid nodules as well as for solitary subsolid nodules.[1,4] A second clinically relevant cutoff diameter is >8 mm. Using data from the NELSON trial, a high lung cancer probability of 9.7% can be estimated for solid nodules ≥8 mm compared to an intermediate probability of about 1% in those smaller than 8 mm (and larger than 5 mm).[2,84]

Nodule growth rate

A growing lung nodule is highly likely to be a malignant one. Individuals with incidentally discovered nodules must always be instructed to present prior imaging studies for comparison, if available, and depending on the time interval, nodule stability practically abolishes the need for any further action. The relatively rapid growth rate of lung cancerous lesions forms the theoretical basis for CT surveillance applied in the management of lung nodules. Volume-doubling time (VDT), although rarely applied in clinical practice, is the most sensitive marker used for growth rate estimation.[85-87] One VDT corresponds to a 26% increase in nodule diameter. The majority of lung cancers present VDTs of up to 400 days, with the highest risk of malignancy associated with VDTs of <100 days.[84-86] However, VDTs of >400 days do not preclude malignancy. In the study of Horeweg *et al.*, the probability of malignancy was significantly increased in participants with VDTs between 400 and 600 days, and lung cancer was diagnosed in 1% of patients with VDTs ≥1000 days.[84] Most of these cases represent lung adenocarcinomas.[88,89] Despite the undeniable importance of growth rate, approximately 20% of nodules ultimately proven malignant actually shrinked at some point during follow-up.[3]

Other predictors of malignant etiology

Spiculation of the nodule anatomical margins has been persistently shown to correlate with an increased risk of lung cancer.[10,38,40,90,91] The majority of lung cancers occur in the upper lobes, and upper lobe nodule location has been identified as predictor of malignancy.[10,38] Other less dominant malignant characteristics are pleural indentation, vascular convergence, and air bronchograms.[92,93]

Predictors of benign etiology

Perifissural nodules, defined as solid nodules in contact with a fissure or the pleural surface,[94] are considered benign, most probably depicting intrapulmonary lymph nodes.[95] In screening cohorts, no patient with such nodules has been diagnosed with lung cancer, even after long-term follow-up.[10,94,96] Therefore, BTS guidelines recommend against further investigation of small (<10 mm), homogeneous, smooth perifissural, and subpleural nodules.[2] The Fleischner society guidelines, on the other hand, specifically state that perifissural or subpleural location does not *per se* definitely abolish the probability of malignancy and morphological (e.g., spiculation or fissure displacement), and clinical risk factors have to be considered for appropriate management.[1]

Calcified lung nodules are generally not considered malignant. However, in an earlier study, calcification was present in 10% of lung cancer cases.[97] Special attention must be paid to the pattern of calcification. Diffuse, central, laminated, and popcorn calcification patterns are predictors of benign etiology.[98] When encountered, they obviate the need for further lung nodule investigation.[2] On the contrary, punctuate, eccentric, and amorphous calcifications are indeterminate patterns that should not be considered as preclusive of malignancy.

Fat attenuation of a pulmonary nodule is almost diagnostic of hamartoma and excludes primary lung cancer as a potential cause.[98]

Recommendations for the Practical Approach of Patients with Lung Nodules

It is recommended that the evaluation of patients with lung nodules should be undertaken by a multidisciplinary team, including pulmonologists, oncologists, radiologists, and thoracic surgeons with expertise in the field. The aim of this multidisciplinary evaluation is to estimate the probability of malignancy and determine the most appropriate management.[1,4] Smoking cessation is strongly advised in all smokers either with incidentally discovered nodules or entering a screening program.[4]

Risk assessment
The diagnostic approach should always start with a detailed evaluation of patient history and imaging studies. Given the multiplicity of relevant clinical and radiological characteristics and the possibility of conflicting influences thereof in an individual patient (e.g., a never smoker with a spiculated, 15-mm upper lobe nodule), several composite malignant risk prediction models have been developed with the use of multivariate logistic regression analysis [Table 3]. Age, smoking status, and nodule diameter are invariably included in all of them, while individual differences reflect discrepancies in the populations used for model derivation.[99-104]

Some of the available guidelines (ACCP, BTS) favor clinical use of prediction models for assigning patients with lung nodules ≥8 mm in diameter in a high- or low-risk group.[2,3] BTS guidelines, for example, recommend the use of Brock model for initial risk assessment, followed by positron emission tomography/CT (PET/CT) scan and the Herder model application in cases of a Brock model risk estimation of ≥10%.[2] However, prediction models have not been clearly shown to perform superiorly than clinical judgment[105,106] and their use is not unanimously suggested. In the most current Fleischner society guidelines, the adoption of prediction models is clearly discouraged.[1] Instead, a dichotomous risk stratification scheme is proposed consisting of a low-risk (<5%) group, associated with younger age, less smoking, smaller, smooth, and nonupper lobe nodules and a high-risk (>5%) group, associated with some or all of the opposite features.

Management of patients with pulmonary nodules
Management options in patients with incidentally detected lung nodules include (a) no further action, (b) CT surveillance in intervals determined by nodule size and clinical risk, (c) further imaging investigation with PET/CT scan, (d) further invasive investigation with nonsurgical biopsies (in most cases CT-guided fine-needle biopsies from peripheral nodules), (e) concurrent definitive histological diagnosis and treatment by means of surgical excision (normally lobectomy or exceptionally sublobar excisions), (f) stereotactic body radiation therapy or radiofrequency ablation in medically inoperable patients, and (g) combinations of the above. Decisions on the most appropriate management option(s) are guided by nodule size, clinical risk of malignancy, patient preferences, and overall health status.[1-3]

The importance of shared decision-making between patients and clinicians could not be overstated. Lung nodule identification is naturally associated with significant anxiety and fear.[107,108] It has been shown that information on the probability of cancer is actually deemed reassuring by most patients;[107] a detailed discussion including expected risks and benefits associated with the different management options promotes adherence to evaluation plans.[109] These needs should be met by the clinician. Moreover, patient preferences must be taken into consideration: some patients find CT surveillance strategies too stressful to bear, when knowing that an even remote probability of malignancy exists, while others would most certainly decide against a surgical operation, unless or even if a definite cancer diagnosis is reached.

The various management recommendations according to nodule size and attenuation, reported in published guidelines, are discussed below and comparatively summarized in Table 4.

Small nodules (<5 or 6 mm)
Small nodules are linked to a very low risk of malignancy, and consequently, no further evaluation is generally warranted. Small size exact definition differs slightly between guidelines. According to the Fleischner society, nodules <6 mm in diameter (or <100 mm³ in volume) are considered small enough to discharge the patient,[1] while the respective cutoff is somewhat lower (<5 mm or <80 mm³) in the earlier ACCP and BTS guidelines,[2,3] based on the results of the study of Horeweg *et al.*, who found that

Table 3: Composite prediction models developed with multivariate logistic regression analysis for malignant risk estimation in individuals with lung nodules

Model	Derivation cohort	External validation	Predictors of malignancy	AUC
Mayo Clinic model[38]	639 patients with newly discovered solitary nodules (4-30 mm) in CXR Single center, USA	Yes	Age Smoking Personal cancer history Nodule diameter Spiculation Upper lobe location	0.83 (derivation) 0.78-0.90 (validation)[99-103]
Herder model[102]	106 patients with indeterminate nodules based on Mayo Clinic model submitted to PET Single center, Netherlands	Yes	As above plus PET findings classified according to FDG avidity	0.92 (derivation and validation)[103]
Veterans Administration model[39]	375 patients with newly discovered solitary nodules (7-30 mm) in CXR Multicenter, USA	Yes	Age Smoking Quit time Nodule diameter	0.79 (derivation) 0.68-0.74 (validation)[99,100,103]
Brock University model[10]	Two cohorts with a total of 2961 current or former smokers submitted to LDCT screening Multicenter, Canada	Yes	Age Gender Family history of cancer Emphysema Nodule size Part solid attenuation Upper lobe location Nodule count Spiculation	0.97 (derivation) 0.90 (validation)[103]
Peking University People's model[40]	371 patients with surgically resected solitary nodules Single center, China	Yes	Age Nodule diameter Clear border Calcification Spiculation Family history of cancer	0.89 (derivation) 0.81 (validation)[99]
TREAT model[104]	606 patients with solitary nodules or masses referred to a thoracic surgeon for suspected or known lung cancer Single center, USA	Yes (same publication)	Age and gender Body mass index COPD (FEV$_1$) Smoking (pack-years) Personal cancer history Preoperative symptoms Lesion size, growth, location Spiculation FDG-PET avidity	0.87 (derivation) 0.89 (validation)

AUC=Area under the receiver operating characteristic curve, FDG=Fluorodeoxyglucose, FEV$_1$=Forced expiratory volume in one second, CXR=Chest X-ray, PET=Positron emission tomography, LDCT=Low-dose computed tomography, COPD=Chronic obstructive pulmonary disease

only nodules <5 mm (or <100 mm³) were not associated with a significantly increased cancer risk.[2,84] These recommendations apply to all solitary and multiple solid nodules.[1,2] In patients with multiple small subsolid nodules, a short-term follow-up CT is warranted [Table 4].

Intermediate solid nodules (<8 mm)
In this case, CT surveillance is invariably recommended,[1-3] based on an estimated cancer risk of 0.5%–2% in high clinical probability screening populations.[10,84] A repeat CT scan 6–12 months (3–6 months for multiple nodules) after baseline, usually followed by a second one at 18–24 months, especially in high-risk patients, is the most recently proposed scheme.[1] Follow-up CT number and intervals differ between guidelines and depending on size and clinical risk [Table 4]. Constantly unchanged nodules after a 2-year follow-up are generally benign[110] and permit discharge of most patients although clear

lack of growth even for as much as 2 years does not definitively preclude malignancy in all cases.[1] In BTS guidelines, volumetric stability is a prerequisite for discharge,[2] given the superior sensitivity of automated or semi-automated three-dimensional volumetric methods for size change assessment compared to standard transverse cross-sectional diameter approach.[111-114] However, volumetric method use in daily clinical practice is still limited. For patients presenting clear evidence of lung nodule(s) growth during the CT surveillance period, further diagnostic assessment should be pursued.

Larger solid nodules (≥8 mm)
Solid nodules ≥8 mm, linked with a risk of malignancy surpassing 2%, necessitate a more aggressive approach. Acceptable alternatives include short initial interval CT follow-up (at 3 months), PET/CT scan, nonsurgical

biopsy, or definite surgical excision.[1] Equivalence of these approaches remains unknown, and choice is usually guided by nodule exact size, location, and morphology as well as patient- (clinical risk factors, comorbidities, suitability for lung resection, and preferences) and health-care system-related (resource availability and local expertise) factors.

Some expert panels have issued more precise recommendations in the form of algorithms. ACCP algorithm begins with a concurrent assessment of lung cancer and surgical risk.[3] Of note, ACCP introduced a concrete qualitative way to define clinical probability of cancer [Table 4]. When surgery is feasible, surgical excision after staging is recommended in high-risk patients. In case of low/moderate probability of malignancy, PET/CT should be performed, and if negative, CT surveillance or nonsurgical biopsy should

Table 4: Comparative presentation of currently published guidelines for the management of patients with lung nodules according to size and attenuation

Guidelines (references)	Nodule(s) size* and attenuation characteristics			
	Small (diameter/volume)	Intermediate solid (diameter/volume)	Larger solid (diameter/volume)	Larger subsolid (diameter/volume)
Fleischner Society[1]	<6 mm/<100 mm³	6-8 mm/100-250 mm³	>8 mm/250 mm³	>6 mm/100 mm³
	Discharge or optional CT at 12 months depending on risk assessment (subsolid nodules necessitate more extensive follow-up at 2 years and 4 years)	Solitary nodules CT at 6-12 months and then at 18-24 months	Solitary nodules CT at 3 months or PET/CT scan, nonsurgical biopsy or surgical excision	Solitary pure ground-glass nodules CT at 6-12 months and then every 2 years for a total of 5 years. Solitary part-solid nodules CT at 3-6 months and then annually for a total of 5 years, if solid component is stable and <6 mm. If solid component is ≥6 mm or growing, proceed to PET/CT scan, nonsurgical biopsy, or surgical excision
	Multiple subsolid nodules CT at 3-6 months and then optionally at 2 years and 4 years	Multiple nodules CT at 3-6 months and then at 18-24 months (optional for low risk)	Multiple nodules CT at 3-6 months and then at 18-24 months (optional for low risk)	Multiple nodules CT at 3-6 months. Further management based on the most suspicious nodule(s)
BTS[2]	<5 mm/80 mm³	5-6 mm CT at 12 months and if stable on volumetry†, discharge. If stable on diameter, repeat at 24 months	≥8 mm/≥300 mm³	≥5 mm
	Discharge	≥6 mm/≥80 mm³ CT at 3 months and if stable or VDT >400 days, repeat at 12 months and then as above	CT surveillance, nonsurgical biopsy, or surgical excision depending on serial risk assessments based on prediction models	CT at 3 months and then further CT surveillance (1, 2, and 4 years) or nonsurgical biopsy or surgical excision depending on risk assessment§

Contd...

Table 4: Contd...

Guidelines (references)	Nodule(s) size* and attenuation characteristics			
	Small (diameter/volume)	Intermediate solid (diameter/volume)	Larger solid (diameter/volume)	Larger subsolid (diameter/volume)
ACCP[3]	<5 mm CT at 12 months (optional for low clinical risk patients)	5-6 mm Low clinical risk‡ CT at 12 months High clinical risk‡ CT at 6-12 months and then at 18-24 months 7-8 mm Low clinical risk‡ CT at 12 months and then at 18-24 months High clinical risk‡ CT at 3-6 months and then at 9-12 months and 24 months	≥8 mm CT surveillance, nonsurgical biopsy, or surgical excision depending on clinical risk (PET/CT should precede further decisions in low-moderate risk patients) In patients with high surgical risk, CT surveillance or nonsurgical biopsy can be chosen depending on clinical risk and SBRT or RFA are recommended as alternatives to surgery	>5 mm Pure ground-glass nodules Annual CT surveillance for at least 3 years (for nodules>10 mm early CT at 3 months followed by nonsurgical biopsy or resection are opted) Part-solid nodules ≤8 mm CTs at 3, 12, and 24 months and then annually for another 1-3 years >8 mm CT at 3 months followed by PET/CT scan, nonsurgical biopsy or surgical excision if persistent (for nodules>15 mm initial follow-up CT should be omitted)

*According to the Fleischner society guidelines, nodule diameter should be calculated as the average of long and short axes rounded to the nearest millimeter. ACCP and BTS guidelines define the reported diameter of a nodule as the maximum one, †BTS guidelines define significant nodule growth as a ≥25% volume change and discern evaluation strategies for growing nodules on the basis of the observed growth rate, as measured by VDT. CT surveillance continuation is proposed for nodules with a VDT >600 days, while a more aggressive workup with PET/CT, biopsy, or surgical excision is deemed necessary for rapidly growing nodules with a VDT ≤400 days. Biopsy or ongoing follow-up with CT is recommended for patients with intermediate VDT (400-600 days) after taking into account patient perspectives, ‡ACCP has introduced a trichotomous qualitative risk assessment model that assigns a high probability of malignancy (>65%) in older heavy smoking individuals with prior cancer and/or larger, spiculated nodules located in the upper lobes. The absence of these characteristics defines low probability of malignancy (<5%), while patients with a mixture of high- and low-risk features are considered to have an intermediate probability (5%-65%), §BTS guidelines are the only to emphasize the use of prediction models for nodule risk assessment. Based on the reported performance of different models, BTS recommends the application of Brock model for an initial algorithmic evaluation of patients with solid nodules >8 mm (or>300 mm³) followed by a second risk assessment using the Herder model in those with a Brock model score >10%. PET/CT scan is included in the Herder model and is, thus, a prerequisite for further evaluation of this group of patients. Follow-up is recommended for those with <10% malignancy risk based either on the Brock or the Herder model, while those with a higher Herder model risk score are candidates for nonsurgical biopsy (10%-70% risk) or surgical excision (>70% risk). Brock model, together with nodule morphology, is also recommended for risk assessment of subsolid nodules ≥5 mm. Of note, Brock model is the only prediction model suitable for multiple nodule risk assessment, as individuals with multiple nodules were included in its derivation cohorts. CT=Computed tomography, PET=Positron emission tomography, ACCP=American College of Chest Physicians, BTS=British Thoracic Society, VDT=Volume-doubling time

follow. If a hypermetabolic lung nodule is detected in PET/CT, surgical resection, preceded or not by biopsy, is the next reasonable step. BTS, on the other hand, has developed a somewhat different algorithm incorporating quantitative prediction models for cancer risk assessment [Table 4].[2]

Patients with multiple solid nodules one or more of which exceeds 8 mm in diameter should be managed according to the most suspicious (or dominant) nodule, which is usually but not necessarily the largest one.[1] Lung metastatic disease is the primary concern in these cases, especially when nodules are located peripherally in the lower lung fields and vary considerably in size.[115] PET/CT may be helpful in these cases.[3]

Larger subsolid nodules (≥5 or 6 mm)

Pure ground-glass and part-solid nodules are less frequently encountered than solid nodules. In two large screening cohorts, ground-glass nodules were found in 15.8% and 9.3% of cases, while part-solid nodules were even less common accounting for 4.3% and 0.9% of all nodules detected.[10] In the same study, part-solid morphology was identified as a significant predictor of malignancy, when compared with solid attenuation pattern, which was not the case for pure ground-glass nodules.[10] Thus, in patients presenting a new solid component during follow-up of initially pure ground-glass nodules, malignancy should be considered highly likely,[116-118] and the more extensive the solid component of the nodule, the higher the risk to represent

invasive carcinoma.[119-121] Total subsolid nodule size has also been linked with the probability of adenocarcinoma occurrence and invasiveness.[122] In series of patients with excised subsolid nodules, ground-glass nodules <10 mm were scantly identified as invasive adenocarcinoma in histological analysis.[123,124] Conversely, in both pure ground-glass and part-solid nodules measuring >10 mm, and even more >15 mm, the probability of malignancy is significantly elevated.[125,126] Specific morphologic features, including bubbly lucencies, air-bronchograms, spiculation, and pleural retraction, are also associated with an increased risk of malignancy and invasiveness.[120,127-129] Another important consideration for subsolid nodules is their association with slowly growing tumors in the spectrum of lung adenocarcinoma (adenocarcinoma *in situ*, minimally invasive adenocarcinoma, and lepidic-predominant invasive adenocarcinoma).[130] This implies that a more prolonged follow-up, extending beyond the usual 2-year time frame, is warranted in subsolid nodules.[1-3] In addition, in contrast to solid nodules, the available options for the evaluation of subsolid nodules are limited by the relative insensitivity of important diagnostic tools, namely PET scan[131,132] and nonsurgical biopsy.[133,134] This holds particularly true for pure ground-glass nodules, while both interventions appear to have a higher diagnostic yield in mixed nodules with a significantly large solid component.[132-134]

Based on the above, CT surveillance is invariably recommended in all patients with solitary subsolid lung nodules measuring ≥6 mm.[1-3] The proposed intervals are shorter for the higher risk part-solid nodules compared to the more indolent pure ground-glass nodules.[1,3] When persistence is confirmed, further CT follow-up for a total of 5 years is recommended for stable ground-glass and smaller part-solid nodules. Persistent solitary part-solid nodules measuring >8 mm in diameter[3] or with a solid component ≥6 mm[1] require a more aggressive workup, including PET/CT (only when solid component is ≥8 mm), nonsurgical biopsy, surgical excision, or combinations. A different approach omitting the discrimination between pure ground-glass and part-solid nodule attenuation is favored by BTS [Table 4].[2]

In patients with multiple subsolid nodules at least one of which is ≥6 mm, follow-up CT at 3–6 months and management focused on the most suspicious nodule are recommended.[1] Infectious and other inflammatory causes are common, but multiple primary lung adenocarcinomas should also be considered.[118] The detection of more than one suspicious nodule raises significantly the likelihood of malignancy. Multiplicity should not preclude a possible definite surgical intervention. Similar proportions of patients with multiple and solitary nodules have undergone surgery and have presented recurrence afterward in published series.[118,135]

Conclusions

Appropriate management of asymptomatic individuals with incidentally discovered lung nodules should balance between potential harm – driven by unnecessary invasive procedures in the case of benign nodules – and the need to diagnose malignant nodules early. This is not always simple or even feasible. All guideline suggested management algorithms take into consideration the pretest clinical probability of lung cancer and CT features of lung nodules. Rates of compliance with these recommendations are, nevertheless, generally low, mainly reflecting complexity. Patient preferences should always be included in management decisions, and multidisciplinary tumor boards are of cardinal importance. Future research should focus on the development and validation of simpler nodule evaluation algorithms, possibly incorporating novel diagnostic modalities, such as molecular signatures, biomarkers, and liquid biopsies.

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