Radiology

Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017[1]

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The Fleischner Society Guidelines for management of solid nodules were published in 2005, and separate guidelines for subsolid nodules were issued in 2013. Since then, new information has become available; therefore, the guidelines have been revised to reflect current thinking on nodule management. The revised guidelines incorporate several substantive changes that reflect current thinking on the management of small nodules. The minimum threshold size for routine follow-up has been increased, and recommended follow-up intervals are now given as a range rather than as a precise time period to give radiologists, clinicians, and patients greater discretion to accommodate individual risk factors and preferences. The guidelines for solid and subsolid nodules have been combined in one simplified table, and specific recommendations have been included for multiple nodules. These guidelines represent the consensus of the Fleischner Society, and as such, they incorporate the opinions of a multidisciplinary international group of thoracic radiologists, pulmonologists, surgeons, pathologists, and other specialists. Changes from the previous guidelines issued by the Fleischner Society are based on new data and accumulated experience.

Online supplemental material is available for this article.

An earlier incorrect version of this article appeared online. This article was corrected on March 13, 2017.

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These revised recommendations for incidentally discovered lung nodules incorporate several changes from the original Fleischner Society guidelines for management of solid or subsolid nodules (1,2). The purpose of these recommendations is to reduce the number of unnecessary follow-up examinations while providing greater discretion to the radiologist, clinician, and patient to make management decisions. Thus, a range of times rather than a specific interval for follow-up computed tomography (CT) is given for many scenarios. This change has been made in recognition of the multiple factors that determine risk and that cannot be easily incorporated into a summary table, as well as the important role of patient preference for either more aggressive or more conservative management. Although we have taken into account new data from the National Lung Screening Trial (NLST), Nederlans-Leuvens Longkanker Screenings Onderzoek (NELSON), International Early Lung Cancer Action Program (iELCAP), Pan-Canadian Early Detection of Lung Cancer Study (PanCan), and British Columbia Cancer Agency (BCCA) cancer screening trials, all of which support the use of less aggressive management of small nodules, we recognize that screening programs have defined protocols to educate candidates about potential risks and the need for consistent monitoring, whereas incidentally identified nodules represent a separate population that requires a more varied approach to clinical management (3–7).

These recommendations refer to incidentally encountered lung nodules detected at CT in adult patients who are at least 35 years old. Separate guidelines have been issued for lung cancer screening, such as those from the American College of Radiology (ACR), and we support the use of those guidelines when interpreting the results of CT screening (8). Specific recommendations are provided for patients with multiple solid and subsolid nodules, and several other commonly encountered clinical situations are addressed.

These guidelines are not intended for use in patients with known primary cancers who are at risk for metastases, nor are they intended for use in immunocompromised patients who are at risk for infection; in these patients, treatment should be based on the specific clinical situation. Also, because lung cancer is rare in children and adults younger than 35 years, these guidelines are not appropriate for such patients. When incidental nodules are encountered in young patients, management decisions should be made on a case-by-case basis, and the physician should recognize that infectious causes are more likely than cancer and that use of serial CT should be minimized. Most nodules smaller than 1 cm will not be visible on chest radiographs; however, for larger solid nodules that are clearly visualized and are considered low risk, follow-up with radiography rather than CT may be appropriate to take advantage of the lower cost and lower radiation exposure.

Our recommendations are summarized in the Table. These are followed by graded ratings of each recommendation using the American College of Chest Physicians recommendations for evidence grading in clinical guidelines (9). Additional explanations are provided regarding the rationale for each recommendation, which is based on the consensus of a multidisciplinary team and a systematic review of the literature, further details of which are included in Appendix E1 [online]. The minimum threshold size for recommending follow-up is based on an estimated cancer risk in a nodule on the order of 1% or greater. This criterion is necessarily arbitrary, and we recognize that a higher threshold may be considered appropriate in some environments and that this threshold will ultimately depend on social and economic factors. Several general considerations regarding technical aspects of using these recommendations are also presented. Finally, in Appendix E1 (online), additional information regarding methods and risk factors is given.

Advances in Knowledge

- For solid nodules, the minimum threshold size for routine follow-up has been increased, and fewer follow-up examinations are recommended for stable nodules.
- For subsolid nodules, a longer period is recommended before initial follow-up, and the total length of follow-up has been extended to 5 years.

Implications for Patient Care

- These guidelines apply to incidental nodules, which can be managed according to the specific recommendations.
- These guidelines do not apply to patients younger than 35 years, immunocompromised patients, or patients with cancer.
- For lung cancer screening, adherence to the existing American College of Radiology Lung CT Screening Reporting and Data System (Lung-RADS) guidelines is recommended.

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Abbreviations:

ACR = American College of Radiology
ACCP = American College of Chest Physicians
BCCA = British Columbia Cancer Agency
iELCAP = International Early Lung Cancer Action Program
NELSON = Nederlans-Leuvens Longkanker Screenings Onderzoek
NLST = National Lung Screening Trial
PanCan = Pan-Canadian Early Detection of Lung Cancer Study

Author contributions:

Guarantors of integrity of entire study, H.M., D.P.N., Y.O., A.A.B.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, H.M., D.P.N., J.M.G., K.S.L., A.N.C.L., J.R.M., A.C.M., Y.O., C.A.P., G.D.R., C.M.S., W.D.T., P.E.V.S., A.A.B.; clinical studies, D.P.N., K.S.L., A.C.M., G.D.R., P.E.V.S.; statistical analysis, K.S.L., A.C.M.; and manuscript editing, all authors

Conflicts of interest are listed at the end of this article.

Fleischner Society 2017 Guidelines for Management of Incidentally Detected Pulmonary Nodules in Adults

A: Solid Nodules*

Nodule Type	Size			Comments
	<6 mm (<100 mm^3)	6–8 mm (100–250 mm^3)	>8 mm (>250 mm^3)	
Single				
Low risk†	No routine follow-up	CT at 6–12 months, then consider CT at 18–24 months	Consider CT at 3 months, PET/CT, or tissue sampling	Nodules <6 mm do not require routine follow-up in low-risk patients (recommendation 1A).
High risk†	Optional CT at 12 months	CT at 6–12 months, then CT at 18–24 months	Consider CT at 3 months, PET/CT, or tissue sampling	Certain patients at high risk with suspicious nodule morphology, upper lobe location, or both may warrant 12-month follow-up (recommendation 1A).
Multiple				
Low risk†	No routine follow-up	CT at 3–6 months, then consider CT at 18–24 months	CT at 3–6 months, then consider CT at 18–24 months	Use most suspicious nodule as guide to management. Follow-up intervals may vary according to size and risk (recommendation 2A).
High risk†	Optional CT at 12 months	CT at 3–6 months, then at 18–24 months	CT at 3–6 months, then at 18–24 months	Use most suspicious nodule as guide to management. Follow-up intervals may vary according to size and risk (recommendation 2A).

B: Subsolid Nodules*

Nodule Type	Size		Comments
	<6 mm (<100 mm^3)	≥6 mm (>100 mm^3)	
Single			
Ground glass	No routine follow-up	CT at 6–12 months to confirm persistence, then CT every 2 years until 5 years	In certain suspicious nodules < 6 mm, consider follow-up at 2 and 4 years. If solid component(s) or growth develops, consider resection. (Recommendations 3A and 4A).
Part solid	No routine follow-up	CT at 3–6 months to confirm persistence. If unchanged and solid component remains <6 mm, annual CT should be performed for 5 years.	In practice, part-solid nodules cannot be defined as such until ≥6 mm, and nodules <6 mm do not usually require follow-up. Persistent part-solid nodules with solid components ≥6 mm should be considered highly suspicious (recommendations 4A-4C)
Multiple	CT at 3–6 months. If stable, consider CT at 2 and 4 years.	CT at 3–6 months. Subsequent management based on the most suspicious nodule(s).	Multiple <6 mm pure ground-glass nodules are usually benign, but consider follow-up in selected patients at high risk at 2 and 4 years (recommendation 5A).

Note.—These recommendations do not apply to lung cancer screening, patients with immunosuppression, or patients with known primary cancer.

* Dimensions are average of long and short axes, rounded to the nearest millimeter.

† Consider all relevant risk factors (see Risk Factors).

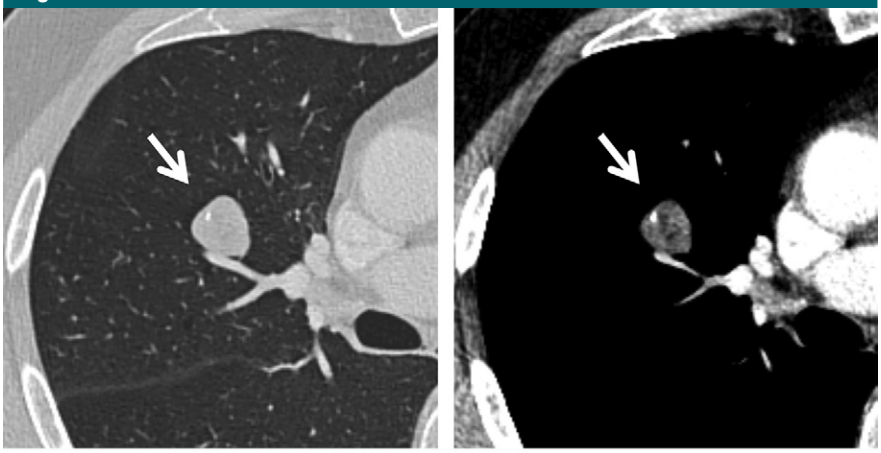
Recommendations for Managing Incidentally Discovered Pulmonary Nodules

General Recommendations

All CT scans of the thorax in adults should be reconstructed and archived with contiguous thin sections (≤1.5 mm, typically 1.0 mm) to enable accurate characterization and measurement of small pulmonary nodules, and routine acquisition and archiving of off-axis (coronal and sagittal) reconstructed series is strongly recommended (grade 1A; strong recommendation, high-quality evidence).

Use of thick sections increases volume averaging, which effectively precludes accurate nodule characterization of small nodules, with respect to part-solid morphology and fat or calcium content, which can affect management (Figs 1–3) (10–12). Coronal and sagittal series facilitate

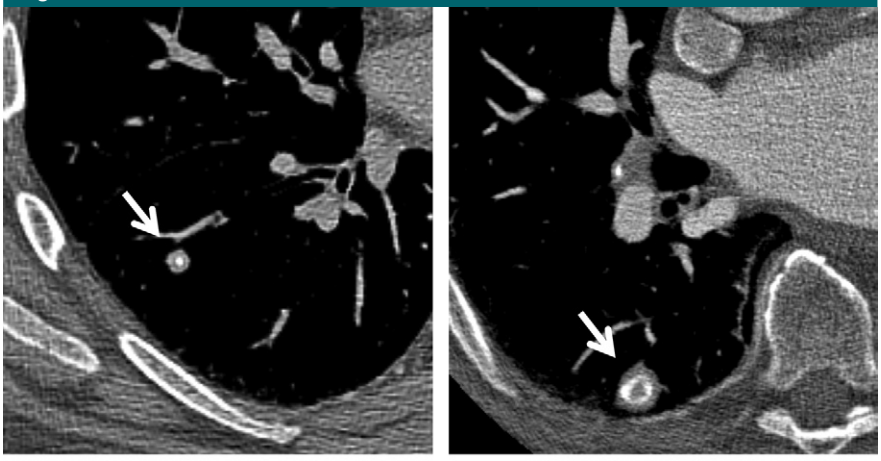
Figure 1



a. b.

Figure 1: **(a)** Lung window and **(b)** soft-tissue window 1-mm transverse CT sections show a smoothly marginated solid nodule (arrow) with internal fat and calcification, consistent with a hamartoma. No further CT follow-up is recommended for such findings.

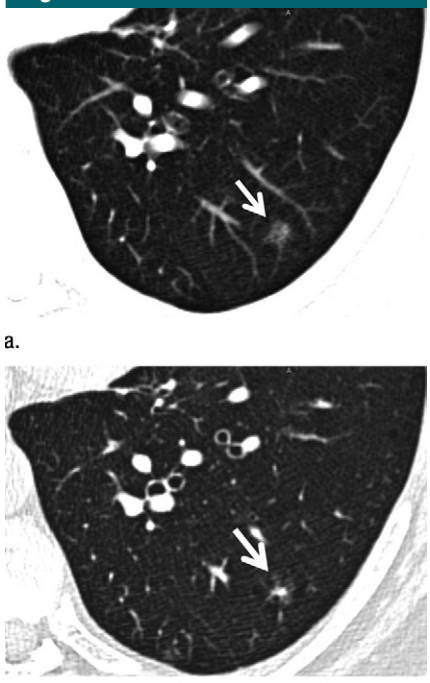
Figure 2



a. b.

Figure 2: **(a)** CT image shows a smoothly marginated solid nodule with central calcification, typical of a healed granuloma. No further CT follow-up is recommended for such nodules. **(b)** CT image shows a smoothly marginated solid nodule with laminar calcification, typical of a healed granuloma. No further CT follow-up is recommended for such findings.

Figure 3



a.

b.

Figure 3: **(a)** Transverse 5-mm CT section shows an apparently pure ground-glass nodule in the left lower lobe (arrow). **(b)** Transverse 1-mm CT section at the same level as **a** reveals that this is a suspicious part-solid nodule with cystic components (arrow).

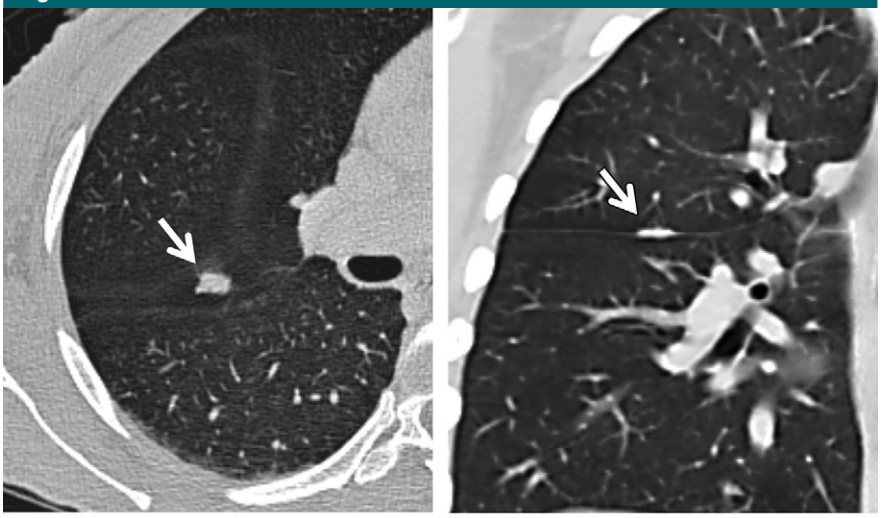
distinction between nodules and scars (Fig 4). This recommendation is not restricted to examinations performed specifically for nodule assessment or lung cancer screening, as lung nodules may be encountered incidentally in any adult patient. If the initial examination was performed with thick sections, a short-term follow-up examination with contiguous thin sections should be considered as a baseline for future comparison.

CT examinations of the thorax performed to follow lung nodules should use a low-radiation technique (grade 1A: strong recommendation, high quality evidence). Techniques to reduce radiation dose are of particular importance, given the frequency with which follow-up CT examinations are performed. We recommend adjusting exposure factors according to body habitus, with a goal of achieving a volumetric CT dose index (or $CTDI_{vol}$) of no more than 3 mGy in a standard-size patient (height, 170 cm; weight, 70 kg), as per ACR recommendations for screening CT (8).

A number of dose reduction techniques, including dose modulation and iterative reconstruction, may be used (13). It is important that a similar technique be used to perform the follow-up examination to minimize interscan variability, with section thickness and reconstruction filter being the most important parameters in this respect.

For these guidelines, manual nodule measurements should be based on the average of long- and short-axis diameters, both of which should be obtained on the same transverse, coronal, or sagittal reconstructed images. Whichever image reveals the greatest

Figure 4



a. b.

Figure 4: **(a)** Transverse 1-mm CT section shows a nodular opacity adjacent to the minor fissure (arrow). **(b)** Coronal reconstructed CT image shows that the opacity is a benign linear scar or lymphoid tissue (arrow).

dimensions is the image that should be used. Measurements should be made with electronic calipers or semiautomated methods and should be recorded to the nearest whole millimeter (grade 1C; strong recommendation, low- or very-low-quality evidence).

Although several screening trials have used the maximum diameter of nodules on transverse sections to estimate size, others (iELCAP) have used the average of long- and short-axis diameters measured by using lung windows (4,5,7,14,15). Prediction models used to estimate malignancy yield better results with the average diameter than with the maximum transverse diameter (16). The Fleischner Society has recommended use of the average diameter since 2005, as the average of long and short axes more accurately reflects three-dimensional tumor volume (1). For larger nodules and for masses larger than 10 mm, it is generally appropriate to record both long- and short-axis dimensions, with the long-axis dimension being used to determine the T factor in lung cancer staging and being a criterion for tumor response to treatment. Measurements should be rounded to the nearest millimeter. Fractional millimeter measurements are not recommended, as their use implies a greater degree of accuracy than that which can be achieved in practice. Thus, the size threshold (<6 mm) corresponds to a rounded measurement of 5 mm or less in these guidelines. As an alternative to manual linear measurements, automated or semiautomated volumetric measurements can be used, and they have the advantage of being more reproducible than manual techniques (17). Volume thresholds of 100 and 250 mm^3 are used for volumetry instead of the 6- and 8-mm thresholds used for linear measurements. However, volumetry is substantially dependent on the specific software used (18,19). For this reason, volumetric measurements to assess nodule growth should be performed with identical software versions. More comprehensive recommendations on nodule measurements, including a full discussion of technical and observer-related factors, will be provided in a separate White Paper from the Fleischner Society that is currently in preparation.

Prior imaging studies should always be reviewed whenever they are available to determine possible growth or stability (grade 1A; strong recommendation, high-quality evidence). Comparisons should include the earliest available study and more recent studies. Note that differences in scanning technique, such as use of thick sections for previous imaging, may make comparison less accurate, especially for small nodules; therefore, routine use of contiguous thin-section reconstruction and archiving is important (20).

Recommendations for Solid Lung Nodules

Recommendation 1: single solid noncalcified nodules.—Solid nodules smaller than 6 mm (those 5 mm or smaller) do not require routine follow-up in patients at low risk (grade 1C; strong recommendation, low- or very-low-quality evidence). There is a paucity of direct evidence regarding cancer probability in small nodules in low-clinical-risk situations. However, there is abundant evidence for cancer risk in current smokers or those who recently quit smoking and who have been studied in the context of lung cancer screening programs. The risk of cancer in patients who have never smoked and in younger patients is known to be significantly lower, with a relative risk on the order of 0.15 in the United States when compared with risk in heavy smokers in the case of solid nodules (21). Given that the average risk of cancer in solid nodules smaller than 6 mm in patients at high risk is less than 1%, it is reasonable to assume an even lower risk in a patient with low clinical risk (7,22). This recommendation is consistent with our policy of excluding nodules with a less than 1% risk of cancer from routine CT follow-up.

Solid nodules smaller than 6 mm do not require routine follow-up in all patients with high clinical risk; however, some nodules smaller than 6 mm with suspicious morphology, upper lobe location, or both may warrant follow-up at 12 months (grade 2A; weak recommendation, high-quality evidence.). These revised guidelines increase the size threshold for routine follow-up of solid nodules to 6 mm. This change is based on supporting data from several screening trials that indicate the risk of cancer in nodules smaller than 6 mm is considerably less than 1%, even in patients at high risk (6,7). On the other hand,

suspicious morphology, upper lobe location, or both can increase cancer risk into the 1%–5% range; therefore, follow-up at 12 months may be considered, depending on comorbidity and patient preferences. Earlier follow-up is not recommended in such instances, as experience has shown that such small nodules, if malignant, rarely advance in stage over 12 months, whereas a short-term follow-up examination showing no apparent change may provide false reassurance. An exception may be made in some patients with technically suboptimal initial scanning results to obtain a high-quality baseline study for future comparison or in nervous patients who may be reassured by evidence of short-term stability.

Solitary noncalcified solid nodules measuring 6–8 mm in patients with low clinical risk are recommended to undergo initial follow-up at 6–12 months depending on size, morphology, and patient preference (grade 1C: strong recommendation, low- or very-low-quality evidence). One follow-up examination should suffice in many instances. If morphology is suspicious or if stability is uncertain, an additional study may be obtained after a further 6–12 months. The risk of malignancy is very low in this category, and not all solid nodules require traditional 2-year follow-up. The recommendation for 2-year follow-up was based on earlier studies with thick CT sections or chest radiographs and was made before the important differences between solid and subsolid nodules were recognized (6,7).

Although some solid cancers have been reported to grow very slowly, with doubling times of more than 700 days and failure to clearly demonstrate growth for up to 2 years, these reports were also based on analysis of thicker-section CT images and evaluation on hard-copy images (23). More recent studies have confirmed the reliability of 2-year stability in the assessment of benignancy in solid nodules, and shorter or longer periods of follow-up may be appropriate in selected subjects, depending on risk factors, nodule morphology, and accuracy of measurements (24). Thus, we recommend optionally discontinuing follow-up of well-defined solid nodules with benign morphology at 12–18 months if the nodule is accurately measurable and unequivocally stable. For subsolid nodules, longer-term follow-up is recommended (2).

For solitary solid noncalcified nodules measuring 6–8 mm in patients at high risk, an initial follow-up examination is recommended at 6–12 months and again at 18–24 months (grade 1B: strong recommendation, moderate quality evidence). This recommendation is based on an estimated average risk of malignancy of approximately 0.5%–2.0% for nodules in this size range and is derived from screening studies, most notably the PanCan, BCCA, and NELSON trials (6,7) Again, the precise intervals can be modified according to individual risk factors and preferences. In some patients in whom nodule stability remains uncertain, further surveillance may be required; however, two follow-up examinations should be sufficient to exclude growth in most subjects.

For solitary solid noncalcified nodules larger than 8 mm in diameter, consider 3-month follow-up, work-up with combined positron emission tomography (PET) and CT (PET/CT), tissue sampling, or a combination thereof; any one of these options may be appropriate depending on size, morphology, comorbidity, and other factors. (grade 1A; strong recommendation, high-quality evidence). Although the average risk of cancer in an 8-mm solitary nodule is only approximately 3% depending on morphology and location, a considerably higher risk can be inferred in certain patients (25,26). As nodules become larger, their morphology becomes more distinct, and management should be strongly influenced by the appearance of the nodule rather than by size alone (Figs 5–7). Thus, both invasive and noninvasive management options are included in this article.

Measurement of attenuation (in Hounsfield units) in solid nodules can be helpful to determine the presence of calcification or fat, either of which can have major diagnostic implications. It is critical that such measurements be made on images without an edge-enhancing filter, such as the type that is generally used on lung and bone images. Measurements on a sharpened image may give erroneously high attenuation values, and other factors, such as beam hardening, can affect the accuracy of the measurements. All attenuation measurements should be made on the thinnest available nonsharpened (typically soft-tissue window) image series; the radiologist should use a small region of interest (not a point

Figure 5

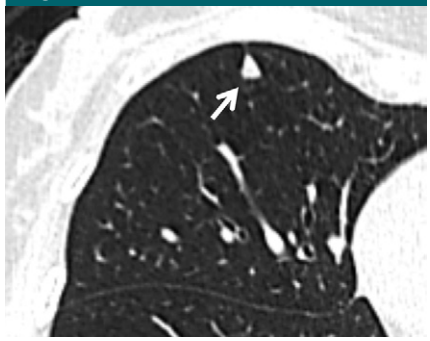


Figure 5: CT image shows a solid triangular subpleural nodule (arrow) with a linear extension to the pleural surface, typical of an intrapulmonary lymph node. No CT follow-up is recommended for such findings.

Figure 6

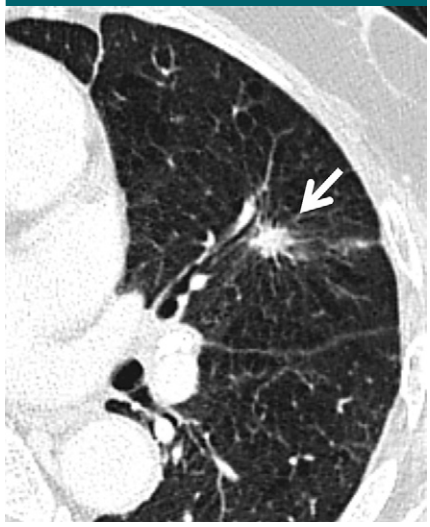
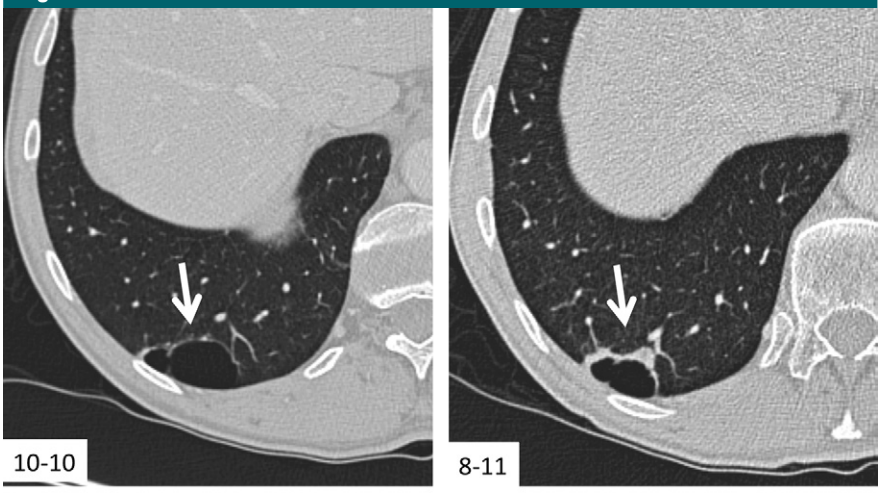


Figure 6: Transverse 1-mm CT section through the left upper lobe shows a suspicious solid spiculated nodule (arrow). Surgery revealed invasive adenocarcinoma.

Figure 7



a. b.

Figure 7: Transverse 1-mm CT sections obtained 10 months apart show a highly suspicious pattern of progressive thickening in the wall of a right lower lobe cyst (arrow). Resection revealed invasive adenocarcinoma.

Figure 8

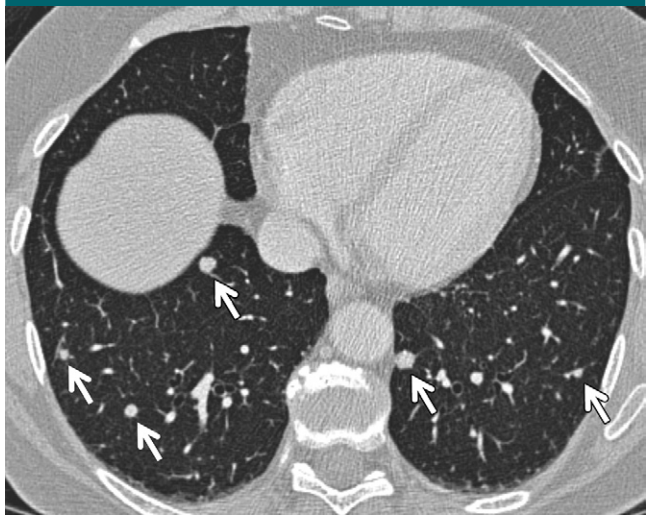


Figure 8: CT image shows multiple solid nodules of varying size with lower zone predominance (arrows) secondary to metastatic thyroid carcinoma.

value) and realize that substantial variations occur among different scanners, filters, and body locations, even with regular calibration (27).

Recommendation 2: multiple solid noncalcified nodules.—For multiple solid noncalcified nodules smaller than 6 mm in diameter, no routine follow-up is recommended (grade 2B; weak recommendation, moderate-quality evidence). Small nodules in this size range are frequently encountered in routine clinical practice and are usually benign in origin. They most often represent either healed granulomata from a previous infection (especially in regions with endemic fungal infections) or intrapulmonary lymph nodes. In patients at high risk, a 12-month follow-up examination may be considered.

Note that this recommendation assumes no known or suspected primary neoplasm that might be a source of metastases. In patients with clinical evidence of infection and in those who are immunocompromised, active infection should be considered, and short-term follow-up may be appropriate.

For multiple solid noncalcified nodules with at least one nodule 6 mm or larger in diameter, follow-up is recommended at approximately 3–6 months, followed by an optional second scan at 18–24 months that will depend on estimated risk. (grade 1B; strong recommendation, moderate-quality evidence). If a larger or more suspicious nodule is present, it should be used as a guide to management according to the guidelines for solitary nodules, as stated previously. In such situations, metastases remain a leading consideration, particularly when the distribution of nodules has peripheral and/or lower zone predominance and when the size of the nodules has a wide range (Fig 8) (28). In most instances, metastases will grow perceptibly within 3 months. An analysis of subjects with multiple nodules in the NELSON trial showed an increase in risk for primary cancer, as the total nodule count increased from 1 to 4, but a decrease in risk for those with five or more nodules, most of which likely resulted from prior granulomatous infection (29).

The dominant nodule should be used as a guide to management; however, additional nodules should also be monitored on follow-up images. In this context, the term *dominant* refers to the most suspicious nodule, which may not be the largest.

Solitary Subsolid Lung Nodules

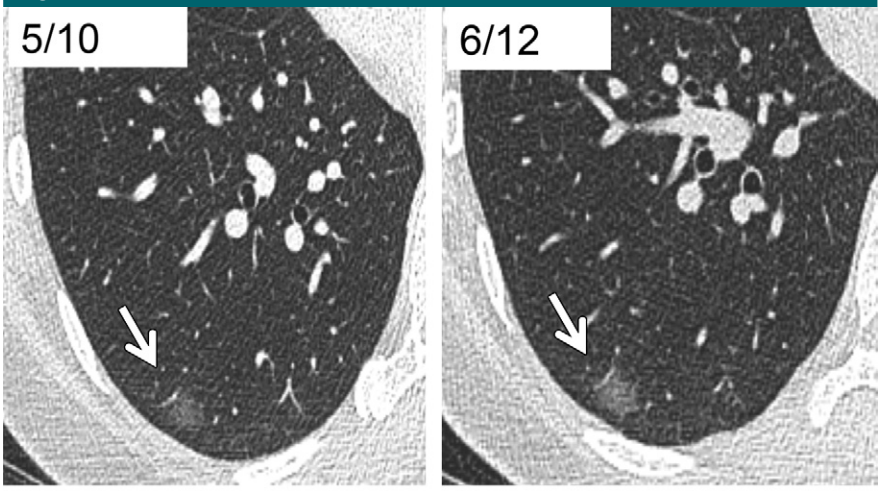
Recommendation 3: solitary pure ground-glass nodules.—For pure ground-glass nodules smaller than 6 mm (ie, 5 mm and smaller) in diameter, no routine follow-up is recommended (grade 1B; strong recommendation, moderate-quality evidence). Because of the high prevalence of ground-glass nodules smaller than 6 mm, we do not recommend follow-up scanning in every patient with such findings. However,

this does not preclude follow-up in selected patients with subsolid nodules (including those with pure ground-glass or part-solid types) close to 6 mm in size with suspicious morphology or other risk factors. This item has been modified slightly from the previous recommendation, providing an option of 2- and 4-year follow-up in selected subjects at high risk. This reflects data from Asian populations, indicating that up to 10% of such nodules may grow and that nearly 1% may progress to adenocarcinoma over many years. However, the finding of malignant transformation in less than 1% of all patients is strong evidence for a conservative approach to the vast majority of these typically noninvasive lesions (30).

For pure ground-glass nodules 6 mm or larger, follow-up scanning is recommended at 6–12 months and then every 2 years thereafter until 5 years (grade 1B; strong recommendation, moderate-quality evidence). The previous recommendation of initial follow-up at 3 months (2) has been changed to follow-up at 6–12 months because earlier follow-up is unlikely to affect the outcome of these characteristically indolent lesions.

To date, numerous reports have shown that pure ground-glass nodules that are 6 mm or larger may be followed safely for 5 years, with an average of 3–4 years typically required to establish growth or, less commonly, to diagnose a developing invasive carcinoma (Figs 9, 10) (30–34).

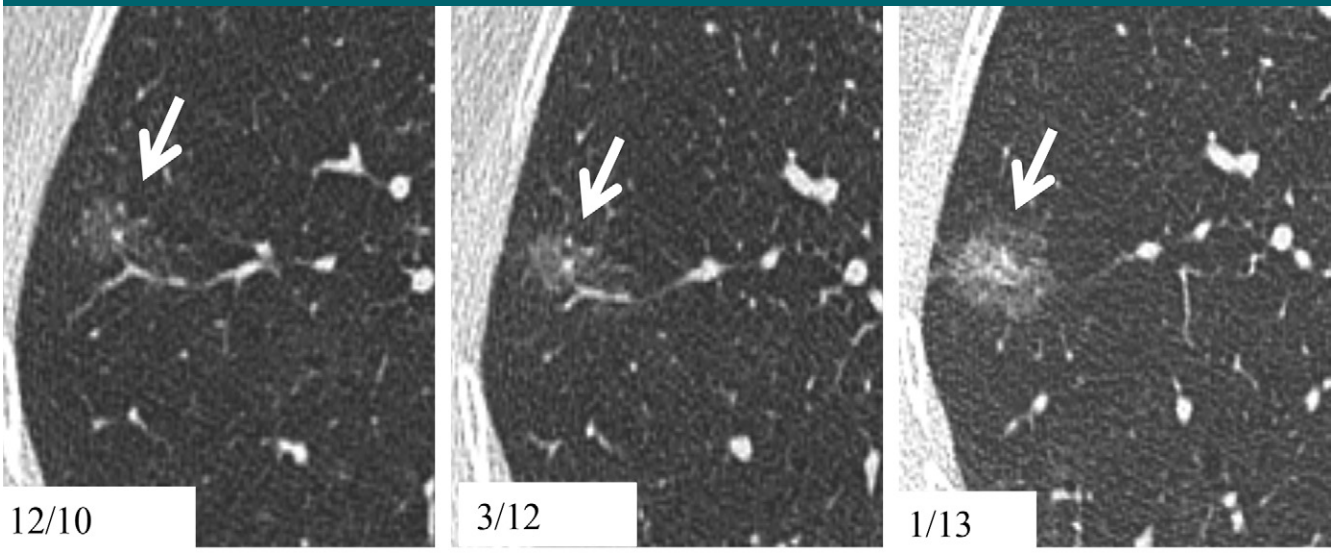
Figure 9



a. b.

Figure 9: Transverse 1-mm CT sections through the right lower lobe. **(a)** A well-defined 6-mm ground-glass nodule (arrow) can be seen. **(b)** Image obtained more than 2 years after **a** shows a subtle increase in the size of the nodule (arrow). This finding was confirmed by noting the slightly altered relationship to adjacent vascular structures. Such subtle progression can be detected only by using 1-mm contiguous sections. Findings are consistent with adenocarcinoma in situ or minimally invasive adenocarcinoma, and continued yearly follow-up is recommended.

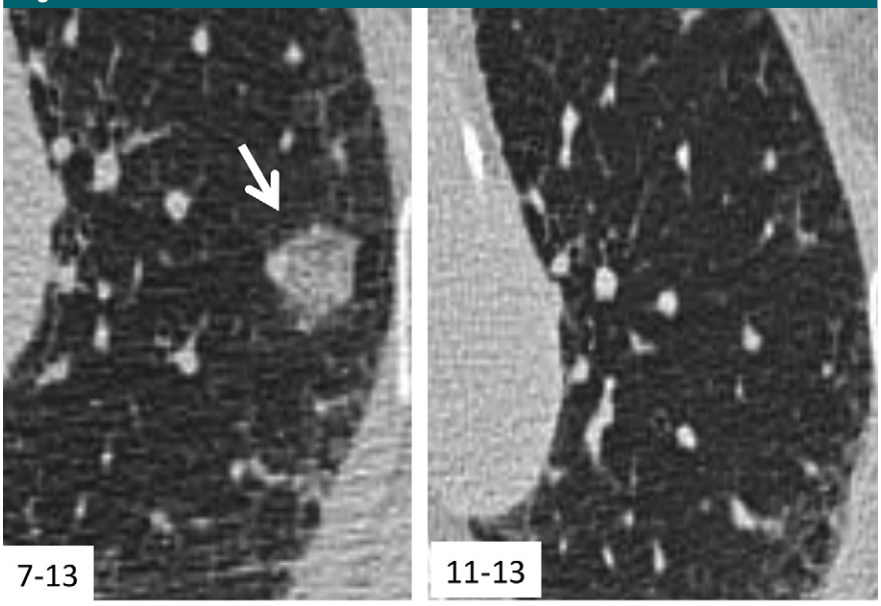
Figure 10



a. b. c.

Figure 10: **(a)** A 1-mm transverse CT image through the right midlung shows a 10-mm pure ground-glass nodule (arrow). **(b)** CT image in the same location as **a** at 15-month follow-up shows only a very subtle increase in opacity. **(c)** CT image in the same location as **a** and **b** a further 10 months after **b** shows the nodule has evolved into a larger part-solid nodule. Surgical resection revealed stage 1A invasive lepidic predominant adenocarcinoma.

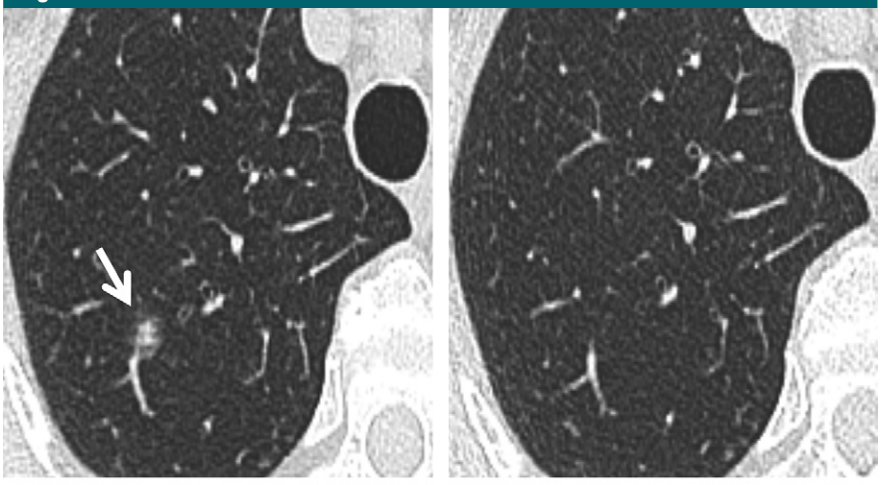
Figure 11



a. b.

Figure 11: **(a)** Transverse 1-mm CT section through the left upper lobe shows an indeterminate 10-mm ground-glass nodule (arrow). **(b)** Follow-up CT image after 4 months shows interval resolution without treatment, consistent with a benign cause, such as focal infection.

Figure 12



a. b.

Figure 12: **(a)** Transverse 1-mm CT section through the right upper lobe shows a 6-mm part-solid nodule with a solid component (arrow) smaller than 4 mm. **(b)** Follow-up CT section at 6-month follow-up shows complete resolution, consistent with a benign cause.

Further evidence in support of conservative monitoring of these lesions has been provided recently by Yankelevitz et al (34), who described a large-scale screening study in which 2392 (4.2%) pure ground-glass (nonsolid) nodules were identified among 57496 baseline studies. From these, a total of 73 lesions subsequently proved to be adenocarcinomas. Overall median time to treatment was 19 months, with solid components developing in 19 (26%) malignant nodules within a median time of 25 months. These all proved to be stage 1 lesions, with an overall survival rate of 100%.

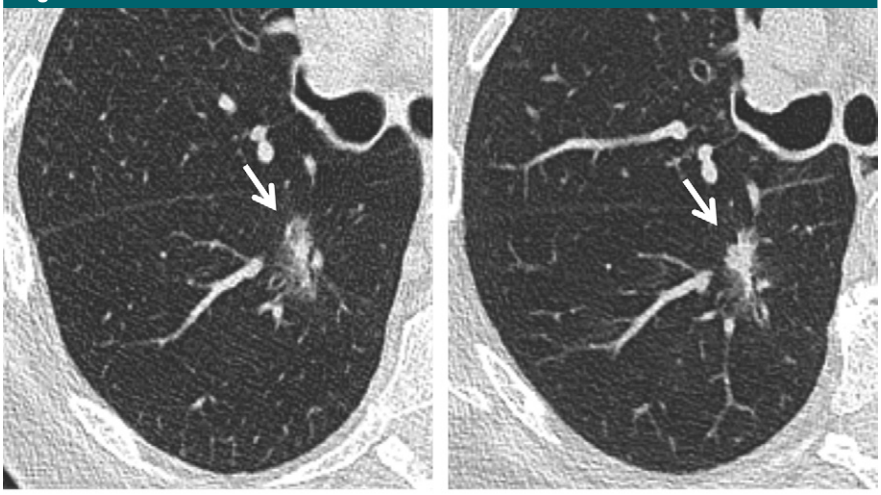
Although these reports represent strong evidence for a conservative approach to pure ground-glass lesions, initial follow-up at 6 months is still recommended, particularly in those nodules with features reported to be risk factors for progression. These include larger lesion size, especially diameter greater than 10 mm (7,35–38), and the presence of bubbly lucencies (35,37,39,40).

Of particular concern are patients who are uncomfortable with the prospect of waiting 12 months for follow-up examinations. In this setting, sooner follow-up may be warranted, as many of these lesions will either resolve or show no change, thereby reassuring the patient (Fig 11) (3,36,41,42). Again, we would emphasize that these guidelines are not intended to preclude either shorter or longer term follow-up in individual subjects, when deemed clinically appropriate (43).

Recommendation 4: solitary part-solid lung nodules.—For solitary part-solid nodules smaller than 6 mm, no routine follow-up is recommended (grade 1C; strong recommendation, low- or very-low-quality evidence). In practice, discrete solid components cannot be reliably defined in such small nodules, and they should be treated similar to the way in which pure ground-glass lesions of equivalent size are treated (see Recommendation 3, which was described previously).

For solitary part-solid nodules 6 mm or larger with a solid component less than 6 mm in diameter, follow-up is recommended at 3–6 months and then annually for a minimum of 5 years. Although part-solid nodules have a high likelihood of malignancy, nodules with a solid component smaller than 6 mm typically represent either adenocarcinoma in situ or minimally invasive adenocarcinoma rather than invasive adenocarcinoma (42,43). Additionally, part-solid nodules may be due to transient infections and may resolve after short-term follow-up (Fig 12) (44). Thus, at least one follow-up scan (3–6 months) is

Figure 13



a. b.

Figure 13: **(a)** Transverse 1-mm CT section through the superior segment of the right lower lobe shows a highly suspicious (large size, ground-glass appearance, and solid morphology) part-solid nodule (arrow). **(b)** Follow-up image obtained 3 months after **a** shows progressive increase in the size of the solid component. Surgery revealed invasive adenocarcinoma.

recommended to determine persistence or resolution. For persistent lesions, yearly follow-up for 5 years is recommended to assess stability of the solid component. The recommended end point of 5 years is necessarily somewhat arbitrary, but it is considered reasonable for patients in whom the dimensions and attenuation of a part-solid nodule have remained unequivocally stable over that time period (42).

For solitary part-solid nodules with a solid component 6 mm or larger, a short-term follow-up CT scan at 3–6 months should be considered to evaluate for persistence of the nodule. For nodules with particularly suspicious morphology (ie, lobulated margins or cystic components), a growing solid component, or a solid component larger than 8 mm, PET/CT, biopsy, or resection are recommended (grade 1B; strong recommendation, moderate-quality evidence.) Abundant evidence enables us to confirm that the larger the solid component, the greater the risk of invasiveness and metastases. A solid component larger than 5 mm correlates with a substantial likelihood of local invasion (7,43,45–54), and this is a threshold criterion in the newly revised T factor staging for adenocarcinoma (Fig 13) (55–57). However, a large solid component can also be seen in transient part-solid nodules (44,58).

Recommendation 5: multiple subsolid lung nodules.—In patients with multiple subsolid nodules smaller than 6 mm, one must consider infectious causes. If lesions remain persistent after an initial follow-up scan at 3–6 months, consider follow-up at approximately 2 and 4 years to confirm stability, depending on the clinical setting (grade 1C; strong recommendation, low- or very-low-quality evidence). For multiple subsolid nodules, including pure ground-glass and part-solid morphologies smaller than 6 mm, short-term (3–6-month) follow-up may be appropriate when the diagnosis is uncertain and the differential diagnosis includes nonneoplastic causes. If stability is established in this time frame, follow-up examinations at 2 and 4 years are recommended to confirm absence of growth, given the likelihood of atypical adenomatous hyperplasia or adenocarcinoma in situ in such instances (34).

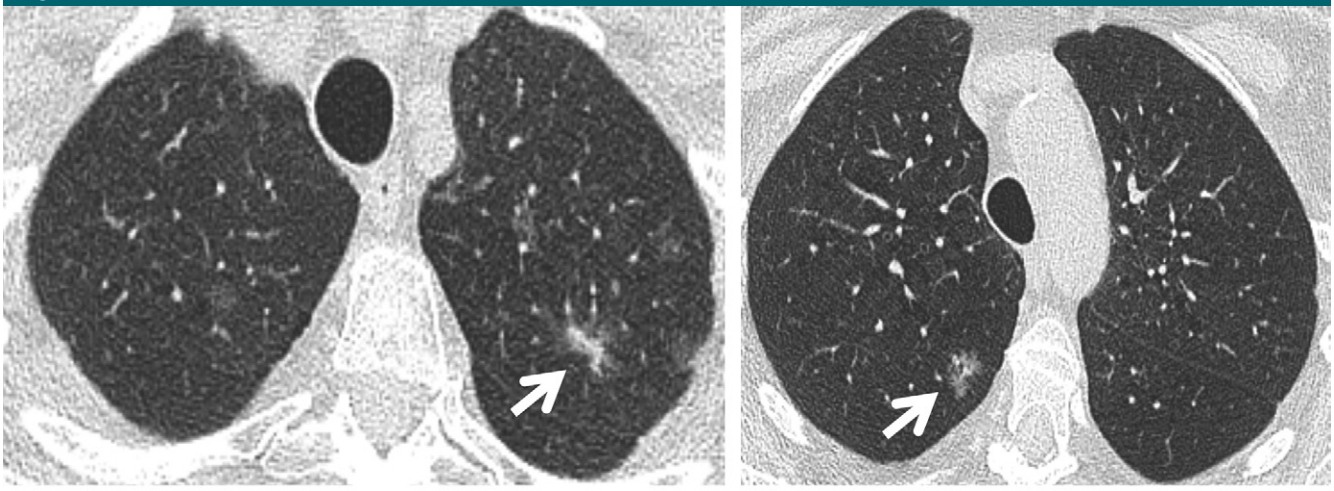
In patients with multiple subsolid nodules with at least one nodule that is 6 mm or larger, management decisions should be based on the most suspicious nodule. In such instances, consider infectious causes. If persistent after 3–6 months, consider multiple primary adenocarcinomas (grade 1C; strong recommendation, low- or very-low-quality evidence). In patients with multiple subsolid lesions 6 mm or larger, the most suspicious nodule (which may not be the largest) should guide management (Fig 14). However, decisions regarding intervention and surgery for a dominant lesion must be constrained by the potential for other existing nodules to grow and require treatment. Also, more than one suspicious nodule increases the overall likelihood of cancer when compared with the likelihood associated with a solitary nodule.

Risk Factors for Malignancy: General Considerations

Nodule Size and Morphology

Nodule size has a clear relationship with risk of malignancy, as discussed previously, and it is a dominant factor in management. In these guidelines, nodules are further divided into solid, ground-glass, and part-solid categories. However, the criteria for making these distinctions have not been completely agreed upon and remain controversial. Van Riel et al (59) examined the agreement between experienced thoracic radiologists using traditional subjective criteria to assign nodules to solid, pure ground-glass, and part-solid categories. Both inter- and intraobserver agreement was found to be highly variable in these nodules. Correct classification of nodules as solid or subsolid by all radiologists was achieved in only 58% of cases (59). Nonetheless, it is generally agreed that nodules that are rendered partially invisible when viewed on thin sections with mediastinal (soft-tissue) window settings and a sharp filter can be regarded as subsolid and that any nodule components other than normal vascular or bronchial structures that remain visible on such images are solid. Small solid or semisolid components that represent early signs of invasive adenocarcinoma may be rendered invisible

Figure 14



a. b.

Figure 14: **(a)** Transverse 1-mm CT section through the upper lobes shows multiple variable-sized subsolid nodules bilaterally, including at least one highly suspicious (large size, ground-glass appearance, and solid morphology) part-solid lesion in the left upper lobe (arrow). Initial follow-up would be appropriate in 3–6 months. **(b)** A more inferior section from the same examination shows another highly suspicious lobulated 10-mm ground-glass nodule in the right upper lobe (arrow), which would also warrant follow up. The findings are most consistent with multifocal primary adenocarcinoma.

with these settings, and the current consensus is that such nodules are best evaluated subjectively by using a lung window setting and an edge-enhancing (sharp) filter to judge the presence and extent of solid components (52,60).

Marginal spiculation has been known for many years to be associated with malignancy, and more recent studies have confirmed spiculation as a risk factor for cancer (7,61). Unfortunately, spiculation has generally been classified in a binary manner as present or absent, and the threshold for determining the presence of spiculation has not been defined. Nonetheless, it has been consistently identified as a risk factor for malignancy, with an odds ratio in the range of 2.2–2.5 in screen-detected nodules (7).

Nodule Location

Lung cancers occur more frequently in the upper lobes, with a predilection for the right lung (62,63). In the PanCan trial, upper lobe nodule location was confirmed as a risk factor, with an odds ratio of approximately 2.0 (7). Adenocarcinomas and metastases tend to be located in the periphery, while squamous cancers are more often found near the hila (62). Small solid nodules in a perifissural or subpleural location often represent intrapulmonary lymph nodes (discussed later in this article).

Nodule Multiplicity

An analysis of patients with multiple nodules in the NELSON trial showed increased risk of primary cancer as the total nodule count increased from 1 to 4 but decreased risk in patients with 5 or more nodules, most of which likely resulted from prior granulomatous infection (29). In the PanCan trial, multiplicity of nodules was associated with a reduced risk of cancer when compared with risk associated with one nodule (7).

Nodule Growth Rate

Cancers have a wide range of growth rates that depend on morphology and histologic findings. Recommended follow-up intervals are intended to minimize the number of examinations and the chance of a growing cancer advancing in stage during the period of CT follow-up prior to diagnosis. Thus, we must consider the potential growth rate of a detected nodule and our ability to detect small changes in size when we make a recommendation for follow-up. Although linear measurement with electronic calipers remains the current standard of practice, experience with semiautomated nodule volumetry suggests that this approach has superior sensitivity in the detection of nodule growth (22,64,65). While robust and validated software for volumetric nodule measurement is not widely used at present, we anticipate that it will have an increased role in the future.

Volume doubling times for solid cancers are well established (one volume doubling corresponds to a 26% increase in diameter), with a large majority of times being in the 100–400-day range. For subsolid cancerous nodules, which represent primary adenocarcinomas, more indolent growth is the rule, with average doubling times on the order of 3–5 years (34,66). For this reason, longer initial follow-up intervals and longer total follow-up periods are recommended for subsolid nodules than for solid nodules.

Emphysema and Fibrosis

The presence of emphysema on a CT image is an independent risk factor for lung cancer (67). An analysis of lung

cancer and emphysema in the NLST trial revealed an incidence of 25 instances of cancer per 1000 screened patients with emphysema, compared with 7.5 instances of cancer per 1000 screened patients for those without (68). Chiles et al (69) investigated the relationship between chronic obstructive pulmonary disease phenotypes and risk of cancer in indeterminate nodules detected in the NLST trial and found that emphysema-predominant chronic obstructive pulmonary disease phenotype and increasing severity of centrilobular emphysema were associated with increased risk of malignancy. Pulmonary fibrosis, particularly idiopathic pulmonary fibrosis, is also an independent risk factor, with a hazard ratio of approximately 4.2 compared with emphysema alone (70).

Age, Sex, Race, and Family History

The relationship between age and lung cancer risk has been clearly established, with an accelerating increase in risk associated with advancing age. Lung cancer is still relatively rare in individuals younger than 35 years and is unusual before the age of 40 years. For each additional decade of life, lung cancer incidence increases steadily (71,72). The possible role of sex as a risk factor for lung cancer has been explored in several recent studies. Chiles et al (69) identified certain individual characteristics of female subjects in the NLST trial, such as lower educational level and lower body mass index, that were associated with an increased risk of cancer; however, the overall 6-year risk of cancer was not significantly different from that in male subjects. Boiselle (73) examined the relative risk for women and men in the same trial with solid, nonsolid, or part-solid nodules and found a significantly higher risk in women with ground-glass (nonsolid) nodules. Female sex was also found to be a risk factor in the PanCan trial, with an overall odds ratio of 1.8; however, the relationship to nodule type was not reported (7). A family history of lung cancer is a risk factor for both smokers and those who never smoked, with an overall relative risk in the range of 1.5 that can extend up to 1.8 in patients with an affected sibling. Race is also a factor, with a significantly higher incidence of lung cancer in black men and native Hawaiian men at low levels of smoking when compared with that in white men (74).

Tobacco and Other Inhaled Carcinogens

Cigarette smoking has been established as the major risk factor for lung cancer since the 1960s, with a 10- to 35-fold increased risk when compared with that in nonsmokers, and exposure to secondhand smoke is a proven, albeit lesser, risk factor (75–77). The association between adenocarcinoma, which accounts for virtually all subsolid lung cancers, and smoking is weaker than the association between small cell or squamous cell carcinomas and smoking, and the incidence of adenocarcinoma in nonsmokers is increasing, with female nonsmokers being affected significantly more often than male nonsmokers (75,77). However, the degree to which smoking affects the risk for lung adenocarcinoma has not been clearly defined; thus, our recommendations for management of subsolid nodules are independent of customary risk categories (78).

A smoking history of 30 pack-years or more and quitting smoking within the past 15 years have been used as the qualifying tobacco exposure threshold for the NLST screening program, and they should be considered indicative of high-risk status in patients with solid nodules. Other inhaled carcinogens that are known risk factors for lung cancer include exposure to asbestos, uranium, or radon (79–81).

Smokeless electronic cigarettes have been introduced, but possible risks associated with these products are as yet unproven (82).

Risk Estimation and Risk Models

These guidelines for nodule management are based on estimations of the individual risk of malignancy. Although nodule size and morphology remain the dominant factors that we use to predict risk, it is important to consider additional clinical risk factors, including smoking, exposure to other carcinogens, emphysema, fibrosis, upper lobe location, family history of lung cancer, age, and sex. Because these factors are numerous and have differing effects on the likelihood of cancer, several sophisticated risk prediction models have been developed (Appendix E1 [online]). However, for the purposes of these guidelines, we recommend that risk be assigned according to the categories proposed by the American College of Chest Physicians (ACCP). Low risk, which corresponds to an estimated risk of cancer of less than 5%, is associated with young age, less smoking, smaller nodule size, regular margins, and location in an area other than the upper lobe. To estimate high risk, we recommend combining the ACCP intermediate-risk (5%–65% risk) and high-risk (>65% risk) categories. High-risk factors include older age, heavy smoking, larger nodule size, irregular or spiculated margins, and upper lobe location. Subjects with intermediate risk share both high- and low-risk characteristics (83).

Invasive Diagnostic and Therapeutic Procedures

These guidelines are limited to the noninvasive management of incidentally detected nodules. The appropriate use of invasive diagnostic and therapeutic procedures is vitally important but depends greatly on available resources and expertise. As a general rule, transthoracic needle biopsy is an effective approach in experienced hands, but it has important limitations for very small nodules and ground-glass lesions due to potential problems with inadequate sampling and false-negative results (84–86).

Newer guided transbronchial tissue sampling techniques that use electromagnetic navigation and endobronchial ultrasonography-guided nodal sampling have greatly extended the role and accuracy of bronchoscopy for diagnosis and staging (87,88), while minimally invasive surgery with lung-sparing technique enables diagnosis and definitive treatment in selected patients (89–92).

Decisions regarding choice of procedure in any given case are best made in the context of a multidisciplinary

conference, where the merits and limitations of each approach can be discussed (93).

Additional Considerations

Apical Scarring

Some degree of pleural and subpleural apical scarring is extremely common, and these scars may have a nodular appearance, especially when viewed on transverse images. Certain features are suggestive of a scar, including a pleural-based configuration, an elongated shape, straight or concave margins, and the presence of similar adjacent opacities. Review on coronal or sagittal reconstructed images can be helpful in the characterization of such findings. Similar considerations apply to subpleural opacities in other locations, including the costophrenic angles, where focal scarring is also common.

Perifissural Nodules

Perifissural nodule is a term used to describe small solid nodules that are commonly seen on CT images adjacent to pleural fissures and that are thought to represent intrapulmonary lymph nodes. Similar nodules can occur in other locations, usually adjacent to a pleural surface. Typically, these are triangular or oval on transverse images, and they have a flat or lentiform configuration in sagittal or coronal reconstructions and a fine linear septal extension to the pleura. When small nodules have a perifissural or other juxtapleural location and a morphology consistent with an intrapulmonary lymph node, follow-up CT is not recommended, even if the average dimension exceeds 6 mm. In one study of patients in the NELSON Lung Cancer Screening Trial, 20% of nodules were classified as perifissural, and 16% of these grew during the study; however, none were malignant (94). However, perifissural or juxtapleural location does not in itself reliably indicate benignancy, and the specific nodule morphology must be considered (95, 96). A spiculated border, displacement of the adjacent fissure, or a history of cancer increase the possibility of malignancy, and a follow-up examination in 6–12 months should be considered in these patients.

Incidentally Detected Lung Nodules on Incomplete Thoracic CT Scans

Lung nodules are commonly encountered in the portions of the lungs that are included on CT scans of the neck, heart, and abdomen, and the question often arises as to whether a complete thoracic CT examination should be performed in such instances.

For most small nodules (<6 mm), we do not recommend any further investigation on the basis of the estimated low risk of malignancy (6,7). For intermediate-size (6–8-mm) nodules, we recommend follow-up CT of the complete chest after an appropriate interval (3–12 months depending on clinical risk) to confirm stability and to evaluate additional findings. If nodule stability can be demonstrated on the basis of retrospective comparison with a previous study, that may suffice. In the case of a large or very suspicious nodule, we recommend proceeding with a complete thoracic CT examination for further evaluation.

Partial Thoracic CT Scans for Nodule Follow-up

We do not recommend use of partial thoracic scans for practical reasons, including the need for a technologist or radiologist to determine the appropriate range of the scan from a scout image and the possible detection of unanticipated abnormal findings that would require complete examination of the thorax to properly evaluate.

Conclusions

These guidelines represent the consensus of the Fleischner Society, and as such, they incorporate the opinions of a multidisciplinary international group of thoracic radiologists, pulmonologists, surgeons, pathologists, and other specialists. Changes from the previous guidelines issued by this society are based on new data and accumulated experience.

The need to consider incidentally detected nodules as a separate well-defined component of standard clinical care is well documented. In a recent survey of thoracic CT studies obtained in adults between 2006 and 2012, more than 4.8 million people underwent at least one thoracic CT examination, with more than 1.5 million nodules identified, and a new lung cancer diagnosis was made in approximately 63 000 patients within 2 years (97). Thus, the importance of a systematic and evidence-based approach to the management of these nodules is apparent.

It is anticipated that these guidelines will remain clinically relevant for many years; however, continued progress in image processing and evolving understanding of the natural history of incidentally identified nodules will likely mandate further revisions in the future.

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