
Management of Solitary Pulmonary Nodules

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Abstract

The workup and management of the solitary pulmonary nodule is an increasingly common and confounding clinical problem for which a uniformly accepted approach has yet to be established. Conventional radiologic literature has suggested a number of imaging characteristics of nodules such as size, cavitation, growth rate, and margin morphology to guide the physician in clinical management. More recent literature emphasizes nodule attenuation, as well as size, growth, etc., in correlation with patient risk factors for disease to guide the most appropriate course of follow-up. Risk factors include age greater than 35 years, smoking history, occupational exposures, and history of malignancy. In this chapter, based on a review of the established recommendations and the authors' clinical experiences, an approach to the management of the solitary pulmonary nodule is put forth.

Keywords

Solitary pulmonary nodule • Nodule management • Lung cancer • Ground-glass opacity • Sub-solid nodule

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Management of solitary pulmonary nodules (SPN) is a vexing clinical issue augmented by rising rate of nodule detection due to more pervasive use of CT imaging in medicine. In addition, newer generation scanners allow for thin-slice imaging of the entire thorax in a few seconds resulting in improved resolution and nodule detection. The role of the radiologist is to help the clinician determine the most appropriate management strategy for these indeterminate and often incidental pulmonary nodules.

The term solitary pulmonary nodule refers to a rounded lesion 30 mm or smaller in diameter with at least two-thirds of its margins

surrounded by lung parenchyma and not associated with atelectasis or lymphadenopathy [1, 2]. On CT imaging, the term focal opacity is frequently encountered encompassing a range of nodules, which may be categorized as solid, semisolid (part solid), or nonsolid (ground-glass). The incidence of SPNs on standard chest radiographs is approximately one in every 500 chest radiographs [3] or 150,000 new cases per year in the United States. Review of eight large lung cancer screening trials revealed a variable prevalence rate of at least one nodule to be 8–51% of which 1.1–12% were malignant [4].

The first concern regarding SPNs is the exclusion of malignancy. The majority of incidental and screen-detected nodules are benign granulomas (both healed and active) (40%) and hamartomas (15%) [5]. Less common causes of benign nodules include nonspecific inflammation and fibrosis, round pneumonia, arteriovenous malformations, healed pulmonary infarcts, hemangiomas, intrapulmonary lymph nodes, tuberculoma, bronchogenic cysts, rounded atelectasis, mucoid impaction, dog “heartworm” (rare) [6], etc. Because bronchopneumonia is a very uncommon cause for SPN, a course of antibiotic therapy in a patient without symptoms is discouraged. It may cause avoidable delays in diagnosis [6]. However empiric antibiotic treatment has been recommended in cases of clustered nodules, which are more likely to represent inflammation rather than malignancy. Follow-up at 1 month after adequate treatment would facilitate distinction of inflammation from a dominant SPN with satellite nodules [1].

The majority of malignant SPNs are lung carcinomas. Imaging features of SPNs, which were subsequently characterized as bronchogenic carcinoma, include poorly defined or spiculated margins, frequently upper lobe location, and corona radiata sign. One-third to 50% may represent metastatic lesions, particularly with a known history of an extrathoracic malignancy [1, 4]. Metastases tend to occur in the subpleural regions of the lower lobes.

Various radiographic features of nodules aid in the estimation of the probability of cancer and thus affect management.

Size

Small solitary pulmonary nodules are likely benign. A screening study by Henschke et al. in 2004 found that none of the detected malignancies were less than 5 mm in diameter [7]. The prevalence of malignancy correlates with nodule size (0–1% for nodules <5 mm, 6–28% for nodules 5–10 mm, 33–60% for nodules 11–20 mm, and 64–82% for nodules greater than 20 mm) [5, 6].

Margins

Margins are classified as smooth, lobulated, spiculated, or irregular. Although most smoothly margined nodules are benign, this feature may be present in up to 21% of malignant nodules [8]. Lobulated contour, signifying uneven growth, is often associated with malignant nodules but can be seen in 25% of benign nodules [9]. A spiculated or irregularly margined nodule displaying a corona radiata sign indicating neoplastic infiltration and distortion on neighboring tissues is almost certainly a sign of malignancy.

Calcifications

Calcifications are found more frequently within benign SPNs. Patterns of calcification characteristic of benign nodules are laminated, dense-central, and popcorn. Stippled, punctate, and eccentric calcifications are suggestive of malignancy [10] (see Fig. 2.1).

Fatty Attenuation

The presence of fat tissue (attenuation between -40 and -120 Hounsfield units) within a SPN is suggestive of a hamartoma. (see Fig. 2.2) Caution is required to accurately measure pixel attenuation within the center of lesion since volume averaging with adjacent aerated lung

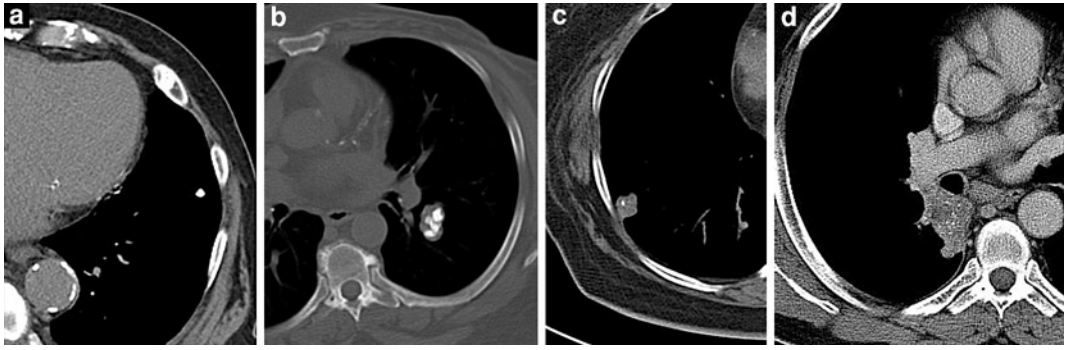


Fig. 2.1 Axial CT images demonstrate varying nodule calcification patterns: **a** dense, **b** popcorn, **c** eccentric, and **d** stippled

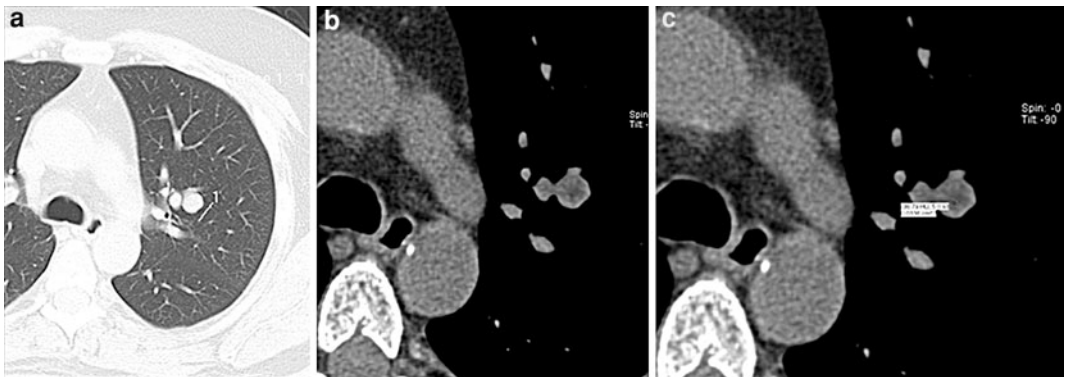


Fig. 2.2 Axial non-enhanced CT images of a left upper lobe 1.4 cm nodule in lung window setting (**a**) and soft tissue window setting on CT (**b**, **c**) measures fatty

attenuation (-36.8 Hounsfield units (HU)), consistent with a hamartoma

may artifactually result in a low-attenuation measurement. Other diagnostic considerations when encountering a SPN containing fat attenuation are lipoid pneumonia and liposarcoma metastases. Correlation with clinical history is usually sufficient to distinguish these two from hamartoma.

carcinoma (BAC). It is the result of lepidic growth, not necrosis, as tumor cells grow along the lung scaffolding sparing the alveoli. Diagnostic considerations for cavitary nodules include pulmonary infarct, fungal infection, Wegner granulomatosis, and solitary metastasis.

Cavitation

Cavitation may be seen with both benign and malignant nodules. Unfortunately, the thickness of the wall is unreliable in distinguishing benign from malignant, although malignancy is associated with thicker and more irregular walls. Pseudocavitation is a descriptor frequently used in describing features of bronchioloalveolar

Attenuation

Careful analysis of the attenuation of SPNs has revolutionized management. There is a correlation between ground-glass attenuation SPNs and histologic findings of adenocarcinoma [11] (see Fig. 2.3). The ground-glass component represents lepidic growth or mucin production. Aoki et al. showed that increasing solid components within a ground-glass nodule correlated

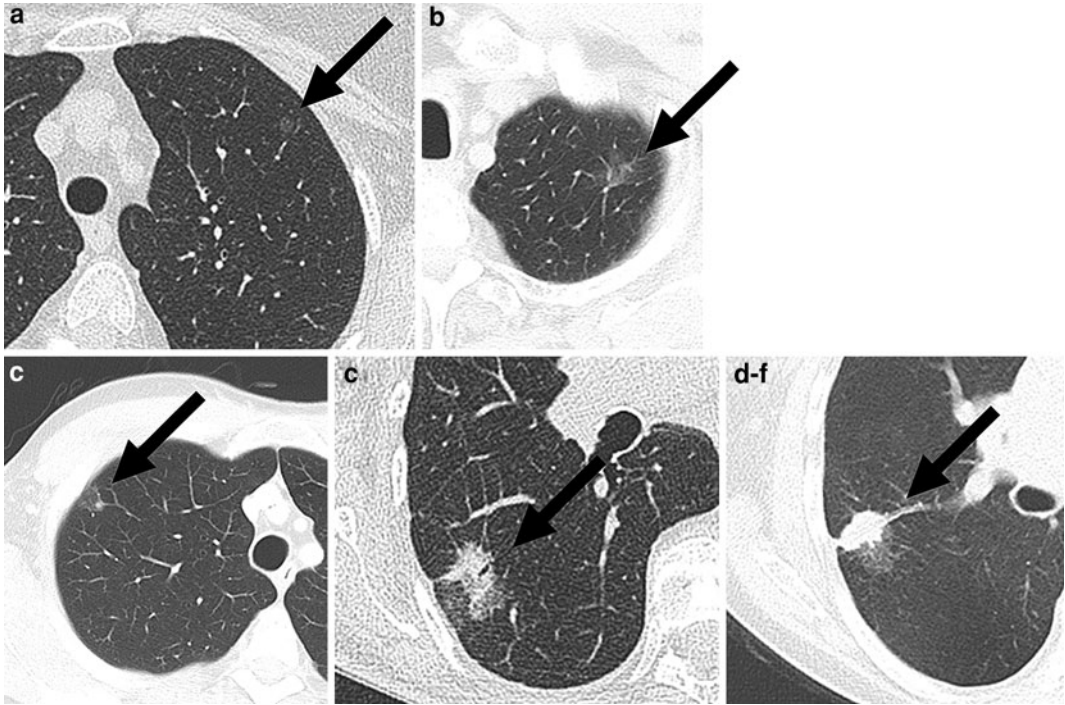


Fig. 2.3 CT appearance of the Noguchi classification of adenocarcinoma of the lung (ground-glass and part-solid nodules). **a** Localized AAH, premalignant. **b** Localized

BAC. **c** Likely mixed BAC/invasive adenocarcinoma. **d-f** Poorly differentiated tubular, papillary adenocarcinoma

with more aggressive behavior [12]. Furthermore, a screening study by Henschke et al. showed a higher rate of malignancy among mixed SPNs (63%) compared with nonsolid (18%) and solid SPNs (7%) [13]. The tumor shadow disappearance rate (TDR) ratio is a measure of the percentage of the SPN that disappears when comparing the size of the nodule on mediastinal versus lung window settings on CT. A correlate of this measurement is the pathologic non-BAC ratio, which measures the percentage of solid component of the mixed attenuation lesion on histologic specimens rather than CT. A study by Lee et al. showed that this pathologic ratio was an independent risk factor for poor prognosis in patients with SPN adenocarcinomas [14]. Differences in the predictive value of the pathologic versus radiologic analysis were likely the result of the ability to

subtract out the scar component within the lesion in the ratio calculation on the histologic analysis.

Growth Rates (Volume Doubling Times)

Volume doubling time (DT) is the time required for a nodule to double in volume. For most malignant SPNs, DT is between 30 and 400 days and corresponds to a 26% increase in diameter. DT may be used to stratify nodules into different categories with differing probabilities for malignancy. For example, nodules with a DT less than 20–30 days are usually acute infectious processes. Slow growing nodules with DT greater than 450 days are likely benign. Lack of two-year growth on chest imaging was thought to confirm benignity. However, this

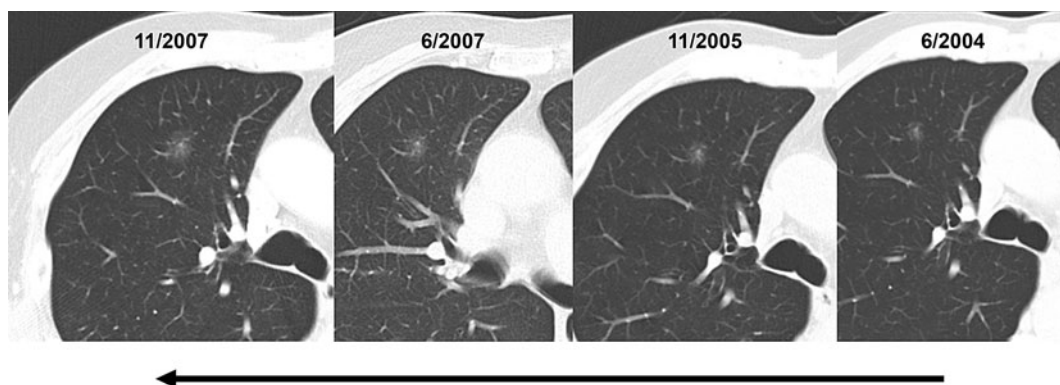


Fig. 2.4 Series of CT images of a right upper lobe ground glass nodule over a period of 3.5 years showed progression in size and density. Subsequent right upper lobe resection confirmed mixed type adenocarcinoma

longstanding dictum on categorization of nodules based on growth measurement has been challenged. Hasegawa et al. [15] reported the DT for malignant SPNs on the basis of their morphologic features: 813 ± 375 days for pure ground-glass opacities, 457 ± 260 days for mixed or partial ground-glass opacities, and 149 ± 125 days for solid nodules. From these data, the two-year stability rule signifying benignity is no longer valid, particularly for pure ground-glass or predominately ground-glass nodules. Appropriate management of these slow growing nodules is an important topic for current investigation.

Preliminary results from a retrospective review of ground-glass attenuation nodules at NYU Langone Medical Center over an 8-year period (2003–2011) showed that 23% of nodules progressed (in size, attenuation, or both) in a median of 14.8 months, with the time to progression as short as 2.8 months and as long as 61.4 months (5 years). Stable ground-glass nodules were followed for a median of 45.8 months (see Fig. 2.4)

Contrast Enhancement

Dynamic contrast-enhanced CT is a tool to assess malignant potential of a SPN. However, this tool is limited to predominately solid

nodules for which contrast enhancement can be reliably measured. This technique may be under utilized given lack of screening potential nodules for this protocol and additional time and supervision required at the time of scan acquisition. Quantitative contrast enhancement consist of repeated imaging of the nodule using contiguous thin collimation sections (1–3 mm) following administration of intravenous contrast administration at a rate of 2 mL/sec. Scans are acquired every 30 s for 5 min, and maximum peak enhancement is measured. Enhancement values <15 HU strongly suggest benignity, whereas enhancement values >20 HU usually indicate malignancy (sensitivity 98%, specificity 73%, diagnostic accuracy 85%) [16]. (see Fig. 2.5). Factors that limit reliability of this technique include small nodule size (<8 mm) and necrosis within the nodule that would underestimate enhancement.

Magnetic Resonance Imaging

Similar to contrast-enhanced dynamic CT, MR has been used to measure peak contrast enhancement and assess the enhancement curve slopes for SPNs. Most benign lesions have a low peak enhancement whereas infections show higher enhancement peak, even higher than those for malignant nodules [17]. However, the

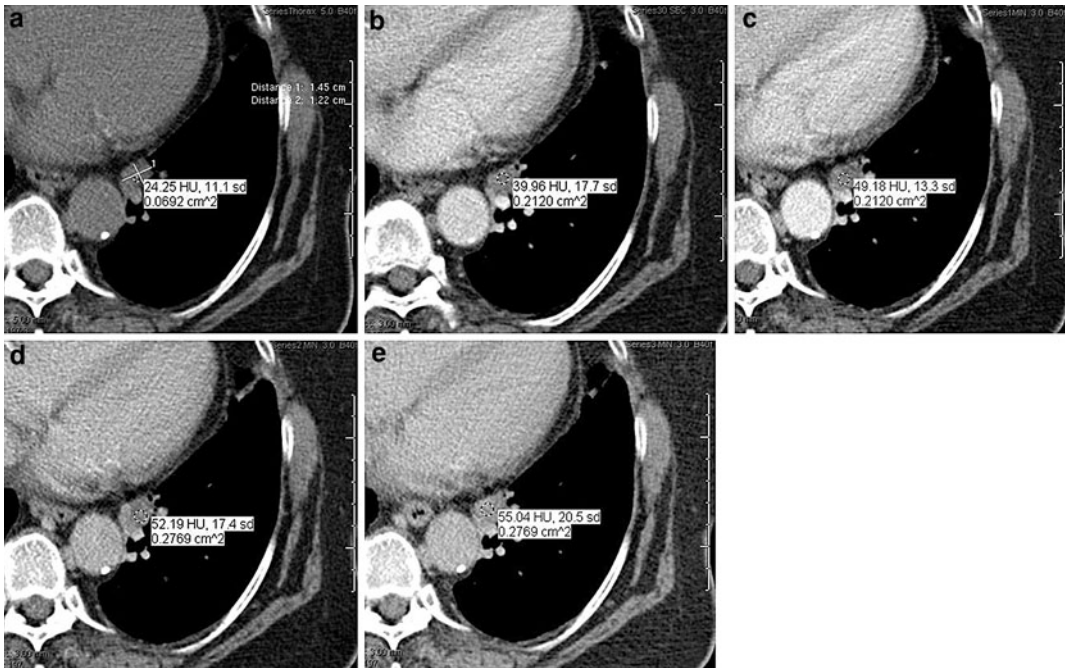


Fig. 2.5 Dynamic contrast enhanced nodule study: sequential CT images through a LLL nodule were obtained precontrast (a) then 30 s (b), 1 min (c), 2 min (d), and 3 min (e) following the start of intravenous

contrast administration. Attenuation measurements of the nodule demonstrate enhancement greater than 15 HU, worrisome for malignancy

lower spatial resolution of MR, somewhat higher cost, lower accessibility, and similar predictive value as dynamic CT contrast-enhanced imaging have made MR less desirable as an assessment tool.

PET-CT Imaging

PET-CT has become commonplace in the assessment of pulmonary nodules that are predominately solid and measure ≥ 8 mm. Reported rates for both sensitivity and specificity are $\geq 90\%$ [18]. However there are limitations to the use of PET. False-positive results may be encountered with infectious and inflammatory processes such as tuberculosis and fungal infections. Dual phase imaging with the first scan obtained at 1 h after injection and the second scan obtained 2–4 h later may improve specificity since infectious and inflammatory processes show

reduced uptake with time whereas malignant lesions continue to accumulate FDG [19]. False-negative results can be seen with bronchioloalveolar carcinoma and carcinoid tumors (see Fig. 2.6). The accepted threshold for standard uptake value (SUV) for malignant nodules is 2.5, although any uptake in a ground-glass or subsolid nodule may suggest malignancy.

Risk Assessment

Calculating the risk of malignancy of an SPN requires not only analysis of nodule size, morphology, location, and growth rate but also defining a patient's underlying risk factors such as age, smoking history, and history of malignancy. A validated model developed by investigators at the Mayo Clinic identified six independent predictors of malignancy in patients with non-calcified nodules measuring between 4 mm and 30 mm

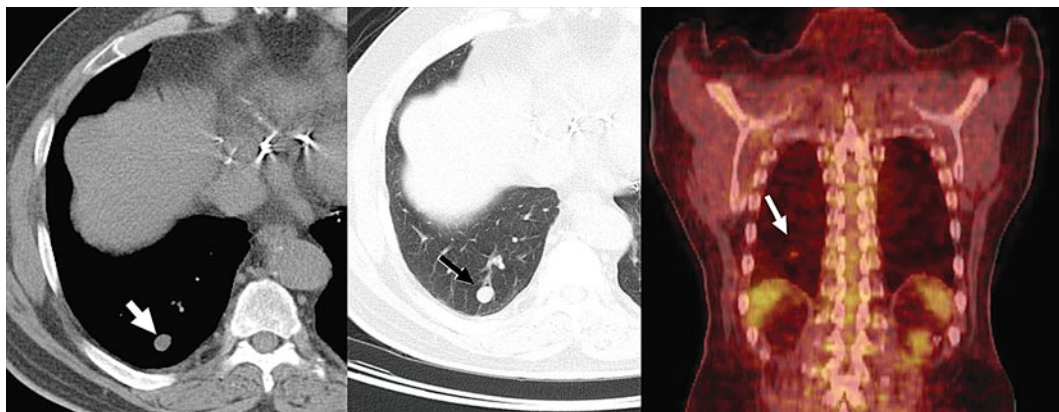


Fig. 2.6 Patient is a 71 year old man with a history of renal cancer treated with surgery and prostate cancer-treated with brachytherapy. Axial CT of the chest demonstrates a round solid 1.2 cm nodule in the right

lower lobe posteriorly. There was mild metabolic activity (SUV 1.0) within the nodule, indeterminate. Subsequent right lower lobe resection revealed a carcinoid tumor

in diameter on chest radiography. Independent predictors of malignancy include age, current or past smoking, history of extrathoracic malignancy, nodule diameter, spiculation, and upper lobe location [20]. Although specific models exist for the calculation of the probability of malignancy of an SPN, they are comparable to the accuracy of expert clinicians' assessments [6].

MacMahon et al. stratified patient's risk levels as low and high as follows: for low risk: age less than 35 years, minimal or absent history of smoking, and no other risk factors [21].

Of note, follow-up CT imaging for a pulmonary nodule should be performed without contrast and utilizing low dose technique (approximately 80 mAs) and thin collimation. Although limited longitudinal coverage is advocated by the Fleischner Society, often the entire thorax is imaged due to logistical and medicolegal reasons.

Recommendations (Adopted from Reference [5])

1. Assess pretest probability (patient's age, smoking history, occupational exposures, nodule size, location, and morphology).
2. For SPN visible on a chest radiograph, compare to previous chest radiographs or other relevant imaging.
3. For SPNs that show growth within the expected time growth for malignancy, tissue diagnosis should be obtained unless contraindicated.
4. If a nodule has 2-year stability, except for patients with pure ground-glass nodules on CT, no additional evaluation recommended.
5. SPN with classic benign calcification pattern, no additional diagnostic evaluation recommended.
6. For every indeterminate SPN on chest radiograph, further characterization with chest CT recommended. Compare to prior CTs if available.
7. Small (<8 mm) solid nodule on CT in a patient without a history of malignancy and at least one risk factor for malignancy (follow Fleischner Society Recommendations [21]):
 - a. ≤ 4 mm: 1 year low dose follow-up CT (no follow-up if stable)
 - b. >4 –6 mm: 6–12 month follow-up low dose CT and again at 18–24 months if stable
 - c. >6 –8 mm: initial follow-up at 3–6 months, then 9–12 and finally at 24 months if unchanged
8. For a solid SPN at least 8 mm in size, dynamic contrast enhancement technique recommended if patient has normal renal function.

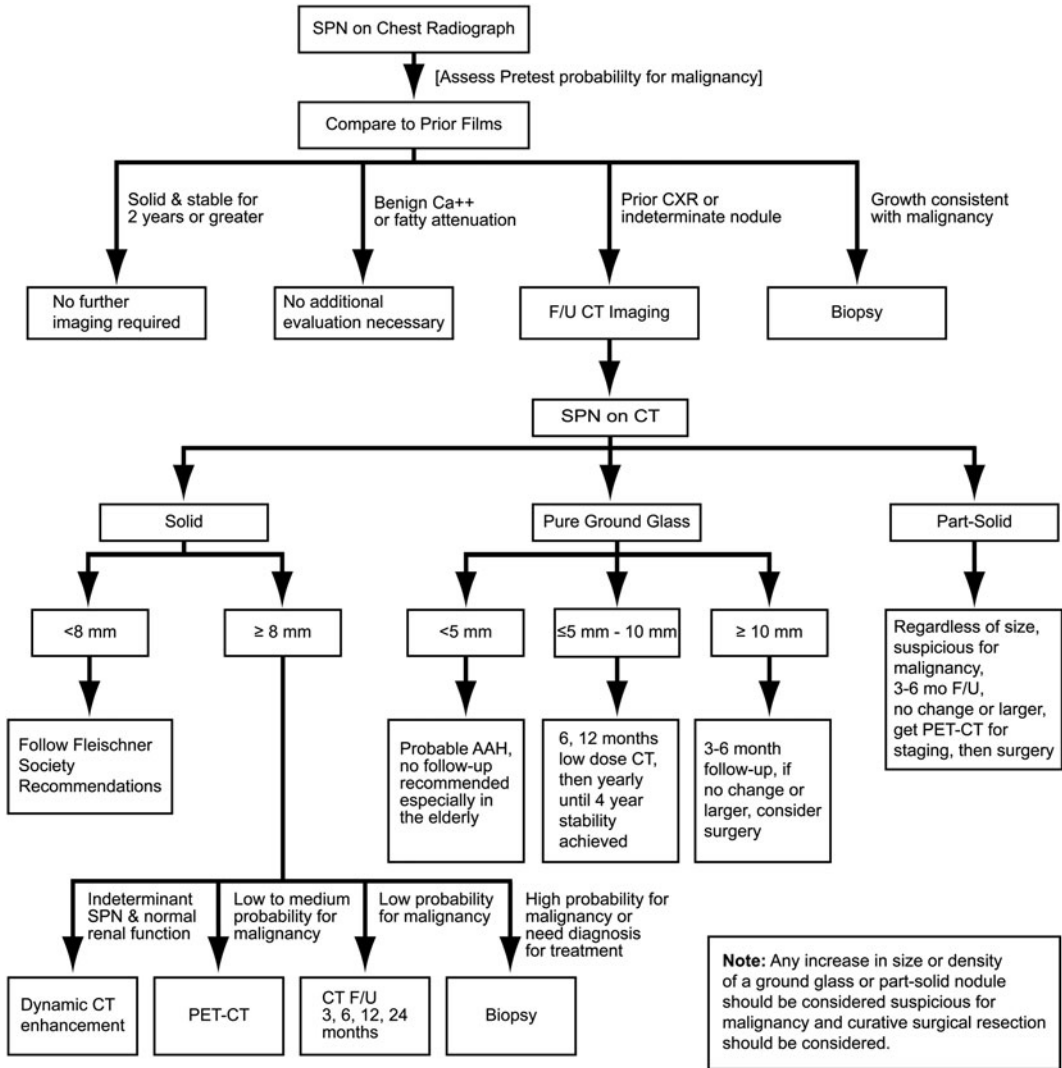


Fig. 2.7 Recommended management algorithm for SPNs

9. For SPN (at least 8 mm in size) with low to moderate pretest probability for malignancy, PET-CT may be helpful given high negative predictive value.
10. Serial (3, 6, 12, and 24 month) follow-up CT imaging may be performed for indeterminate (≥ 8 mm) SPNs if
 - a. Patient is a candidate for curative surgery
 - b. Clinical probability of malignancy is low
 - c. SPN is not hypermetabolic on PET
 - d. SPN peak enhancement is < 15 HU
 - e. Patient prefers a non-aggressive approach
11. Needle biopsy should be considered when
 - a. Discordant clinical pretest probability and imaging findings
 - b. Suspected benign diagnosis requires treatment (i.e. tuberculosis or fungal infection)
 - c. If proof of a malignant diagnosis required prior to surgery or radiation therapy
12. For ground-glass and part-solid nodules, recommended follow-up based on NYU preliminary research data on ground-glass nodule progression (described above) and published recommendations by Godoy and Naidich [22] (see Fig. 2.7).

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