Subsolid Pulmonary Nodules and the Spectrum of Peripheral Adenocarcinomas of the Lung:
Recommended Interim Guidelines for Assessment and Management[1]

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Pulmonary nodule characterization is currently being redefined as new clinical, radiologic, and pathologic data are reported, necessitating a reevaluation of the clinical management, especially of subsolid nodules. These are now known to frequently, although not invariably, fall into the spectrum of peripheral adenocarcinomas of the lung. Strong correlation between the Noguchi histologic classification and computed tomographic (CT) appearances of these lesions, in particular, has been reported. Serial CT findings have further documented that stepwise progression of lesions with ground-glass opacity, manifested as an increase in size or the appearance and/or subsequent increase of solid components, does occur in a select subset of patients. As a consequence, recognition of the potential association between subsolid nodules and peripheral adenocarcinomas requires a review of current guidelines for the management of these lesions, further necessitated by a differential diagnosis that includes benign lesions such as focal inflammation, focal fibrosis, and organizing pneumonia. Specific issues that need to be addressed are the need for consensus regarding an appropriate CT classification, methods for precise measurement of subsolid nodules, including the extent of both ground-glass and solid components, as well as accurate assessment of the growth rates as means for predicting malignancy and prognosis. It is anticipated that interim guidelines may serve to standardize our current management of these lesions, pending further clarification of their natural history.

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Radiology

Recent advances in technology, including widespread availability of multidetector computed tomographic (CT) scanners associated with an abundance of new information obtained especially from low-dose CT lung cancer screening programs, have increased our understanding of the varieties of small peripheral lung nodules encountered in daily clinical practice, in particular, the importance and prevalence of subsolid pulmonary nodules (1,2).

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Essentials

- Subsolid nodules are now known to frequently represent the histologic spectrum of peripheral adenocarcinomas, including premalignant atypical adenomatous hyperplasia (AAH), bronchioloalveolar carcinoma (BAC), and mixed subtype adenocarcinoma; on the basis of current knowledge, new guidelines are proposed for follow-up and management of subsolid nodules on CT scans.
- Isolated lesions with pure ground-glass opacity (GGO) that are less than 5 mm in size do not necessarily require follow-up CT studies since they nearly always represent foci of AAH; for those between 5 and 10 mm, follow-up is requisite pending better definition of their true nature.
- Nodules with pure GGO that are larger than 1 cm in size should be assumed as BAC or invasive adenocarcinoma provided persistence for at least 3 months, although 20%-25% will prove to be benign at resection; surgery should be considered especially if the nodule is enlarging or if there is an increase in attenuation or development of a solid component.
- Lesions with mixed solid component and GGO should also be presumed malignant and surgical resection should be considered, again provided lack of interval change over at least 3 months.

Pending potential revisions in pathologic classification of these lesions, this includes premalignant atypical adenomatous hyperplasia (AAH), bronchioloalveolar carcinoma (BAC), and mixed subtype adenocarcinoma (3).

In this review we focus on clinical, radiologic, and pathologic aspects of subsolid pulmonary nodules, with the intention to propose new interim management guidelines.

Epidemiology of Adenocarcinoma of the Lung

Lung cancer continues to be the leading cause of cancer-related death in both men and women in the United States (4). Adenocarcinoma is the most common type of lung cancer, representing 30%–35% of all primary lung tumors, and its incidence has increased over the past few decades (5,6). Included in the spectrum of adenocarcinomas of the lung (3,7), BAC consists of a peripheral tumor with distinct epidemiology and clinicopathologic and radiologic features, accounting for 2%–6% of all non–small cell lung cancers (8). When BAC is added to mixed subtype adenocarcinoma with a BAC component, their combined incidence reaches up to nearly 20% of all lung cancers (5,6,8).

BAC presents a unique growth pattern along alveolar septa without stromal invasion and has an indolent course (8). It is less commonly associated with smoking, when compared with other non–small cell lung cancers (although smokers are at increased risk of all types of lung cancer, regardless of histology), has a higher incidence in women, and has a younger age distribution (8–10). The presence of other pulmonary diseases, such as fibrotic disorders, increases the risk of developing BAC (8). BAC also contrasts with other forms of lung cancer by exhibiting a relatively high incidence of multifocality (25% vs 5%) (5). More recently, it has also been shown that adenocarcinomas, including those with BAC features, disproportionately respond to treatment with tyrosine kinase inhibitors (11).

The incidence of BAC is higher in Japan than in other parts of the world, including the United States or Europe (3). In the United States, there is evidence that the incidence of BAC has increased four-fold from 1955 to 1990, with much of the increase in BAC occurring in women (5).

Histopathologic Classification of Adenocarcinoma of the Lung

In 1995, Noguchi et al (12) proposed a histologic classification for small peripheral adenocarcinomas, including six subtypes, on the basis of the patterns of tumor growth. Type A corresponds to localized BAC; type B, localized BAC with foci of collapsed alveolar structures; type C, localized BAC with foci of active fibroblastic proliferation; type D, poorly differentiated adenocarcinoma; type E, tubular adenocarcinoma; and type F, papillary adenocarcinoma with evidence of compressive and destructive growth. Types A, B, and C represent a distinct grouping, as they show in common a predominant growth pattern involving "replacement" of alveolar lining cells. Type C, although denominated BAC according to prior criteria, is differentiated from types A and B by the presence of foci of active fibroblastic proliferation, indicating a more advanced form of the disease, with stromal invasion (12). In distinction, types D through F represent "non-replacement" invasive adenocarcinomas and, as initially proposed by Noguchi et al, likely arise de novo, distinct from types A through C. In this seminal study, types A, B, and C represented the most common forms of adenocarcinoma (74%).

Since Noguchi et al first proposed this classification, substantial changes have been made in the World Health Organization subclassification of lung adenocarcinomas, reflecting better understanding of the histopathologic features of this disease (3). A major change made in the 1999 classification and maintained in the 2004 classification was the addition of AAH (Fig 1) as a premalignant lesion (3). As documented at histologic evaluation of resected lung cancers, these lesions have been identified accompanying adenocarcinomas in up to 60% of cases (13–15).

Three subtypes of BAC are now recognized: mucinous (Fig 2a), nonmucinous (Fig 2b), and mixed mucinous and nonmucinous, or indeterminate. Importantly, in accordance with the 2004 World Health Organization classification, to be classified as BAC, tumors must show pure lepidic growth, defined as growth of neoplastic cells along pre-existing structures, without stromal, pleural, or vascular invasion (3,16). As defined, this corresponds to Noguchi type A and B lesions only. In terms of distinction, any tumor that manifests as BAC with an invasive component (Fig 3) is termed *adenocarcinoma, mixed subtype* (16), corresponding to Noguchi type C lesions. It is now documented that most adenocarcinomas are heterogeneous and consist of more than one subtype, with mixed subtype adenocarcinoma being most frequently diagnosed (3).

Peripheral Adenocarcinoma: CT-Pathologic Correlations

Currently, pulmonary nodules are characterized at CT as either solid or subsolid. Solid nodules are defined as those that completely obscure the lung parenchyma. In distinction, subsolid nodules include both pure ground-glass opacities (GGOs) and mixed solid component and GGO. GGOs are defined as focal nodular areas of increased lung attenuation through which normal parenchymal structures such as airways, vessels, and interlobular septa can be defined. Nodules

with mixed solid component and GGO, or part-solid nodules, by definition present both ground-glass and solid components (1).

To date, most studies correlating pathologic with CT findings in patients with peripheral adenocarcinomas of the lung have focused on the Noguchi classification, for which excellent although imperfect correlations have been well documented (Fig 4) (17–20); hence, the rationale for maintaining familiarity with this classification (Table). Following this classification, foci of AAH appear as lesions with GGO that typically measure less than 5 mm in size, although these lesions may be as large as 1–2 cm (13,14). In turn, Noguchi type A and B lesions, which demonstrate purely lepidic growth pattern, typically manifest as nodules greater than 5 mm in diameter with pure GGO. In distinction, Noguchi type B lesions showing evidence of structural collapse may also manifest as predominantly subsolid lesions with GGO with a small solid component, while Noguchi type C lesions showing fibroblastic proliferation with stromal invasion correlate with lesions with mixed solid component and GGO, with still more extensive solid components than seen in Noguchi type B lesions (9,17). As will be discussed later, progression of lesions from those with pure GGO to

those with mixed solid component and GGO has been shown to occur in select cases, correlating as predicted to stepwise progression of Noguchi replacement-type adenocarcinomas (21,22).

Unlike Noguchi types A, B, and C lesions, Noguchi types D, E, and F lesions histologically correspond to purely invasive adenocarcinomas and typically manifest either as solid or near completely solid pulmonary nod-
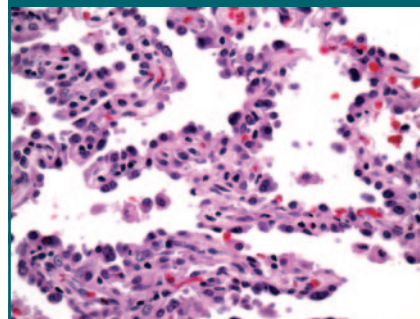
Figure 1

Figure 1: Photomicrograph demonstrates AAH. Alveolar wall is slightly thickened and lined by a single layer of cuboidal cells with mild to moderate nuclear atypia. It is apparent why these lesions present as subtle, often difficult to identify, small GGOs. (Hematoxylin-eosin stain; original magnification, ×400.)
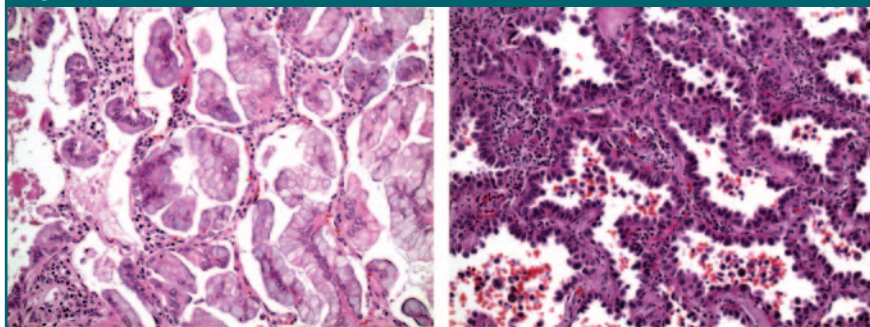
Figure 2

a.   b.

Figure 2: **(a)** Photomicrograph demonstrates BAC, mucinous type. Columnar cells show lepidic growth pattern, with tumor cells mantling pre-existing alveolar septa. These cells contain abundant cytoplasmic mucin. No stromal invasion is seen. (Hematoxylin-eosin stain; original magnification, ×200.) **(b)** Photomicrograph demonstrates BAC, nonmucinous type. Alveolar wall is thickened and lined by a single layer of atypical cuboidal to columnar cells. No stromal invasion is seen. (Hematoxylin-eosin stain; original magnification, ×200.)

ules that range from well-defined to irregular, spiculated lesions at CT (17).

Yang et al (18) in a seminal study correlated Noguchi types A, B, C, and D lesions with four thin-section CT patterns: pure GGOs; heterogeneous GGOs, a subset of lesions with pure GGO in which either reticular opacities or air alveolograms or bronchiolograms can be identified (Fig 5); mixed nodules with a central solid component and a ground-glass halo (Fig 6); and solid nodules, respectively. On the basis of this CT classification, pure GGOs could be categorized as type A in 94% of cases, heterogeneous GGOs proved to represent type B lesions in 71% of cases. Type C lesions proved to be those with mixed solid component and GGO in 29% of cases and solid nodules in 50%, while all type D lesions proved to be solid nodules. Not unexpectedly, as might be predicted on the basis of the underlying histologic features, among the so-called replacement-pattern lesions (Noguchi types A to C), type C lesions were substantially larger and had higher attenuation than type A and B lesions, with less extensive ground-glass component and absent air alveolograms or bronchiolograms (18).

Despite reported close correlations, however, it is apparent that considerable overlap exists between CT appearances (24,25), with differentiation between AAH, especially when lesions are greater than 5 mm in size, BAC, and minimally invasive adenocarcinoma especially problematic.

Oda et al (26), for example, evaluated 52 nonsolid nodules that included 35 BACs and 17 AAHs. According to multivariate analysis, nodular sphericity was shown to be substantially more often associated with AAH, whereas internal air bronchograms proved to be highly suggestive of BAC. Although AAH has been reported characteristically to be smaller than 10 mm in size (19), in this study, size was shown to be an inaccurate predictor differentiating AAH from BAC, as 47% of AAHs measured more than 10 mm and 14% of BAC lesions measured less than 10 mm (26).

Perhaps most important, it has also been reported that although nonsolid nodules with pure GGO are likely to represent either AAH or BAC, they may rarely represent invasive adenocarcinomas (Fig 7). Nakata et al (19), for example, have reported that 7% of nonsolid nodules measuring less than 1 cm proved to be mixed subtype adenocarcinomas. It is also worth emphasizing that the distribution of histologic subtypes and CT appearances varies when solitary lesions are compared with multiple lesions, although the implications of these differences remain unclear. Kim et al (27), for example, in a retrospective study comparing multiple ($n = 105$) with solitary ($n = 31$) subsolid nodules found that both AAH ($P = .001$) and BAC ($P = .029$) proved significantly more likely to be present in patients with multiple lesions, whereas adenocarcinomas proved more frequent in solitary subsolid nodules ($P < .001$).

Given the differences among these reports, not surprisingly, additional approaches emphasizing use of quantitative densitometric methodologies to differentiate between AAH, BAC, and mixed type adenocarcinoma have been proposed (28,29). Although suggestive, these findings require further validation prior to routine acceptance.

CT-Pathologic Correlations: Prognosis

Equally important to the observation of a close correspondence between CT appearances and the Noguchi classification is the demonstration of close correlation with prognosis. As documented by Noguchi, type A and B lesions are rarely associated with lymph node metastasis or vascular or pleural invasion and demonstrate low mitotic rates, resulting in 5-year survival rates of nearly 100% (12). Type C lesions typically show a higher rate of lymph node metastasis, vascular and pleural invasion, and a higher mitotic rate corresponding to a lower 5-year survival rate of 74.8% ($P < .01$) (12). In distinction, types D to F adenocarcinomas proved to have a significantly less favorable prognosis, resulting in a 5-year survival of approximately 50%. More recent histopathologic studies have further documented these initial observations (30).

Further validation of the prognostic significance of the percentage of BAC and non-BAC components of adenocarcinomas has recently been shown, even when compared with the presence of epidermal growth factor receptor gene mutations, which are known to be associated with BAC component and to correlate with tumor sensitivity to tyrosine kinase inhibitors (31,32). Kobayashi et al (32), in a study that evaluated 127 patients with pathologic stage 1A adenocarcinomas of the lung (≤20 mm), reported that tumors with high percentage of non-BAC component are a sufficient risk factor for both recurrence and poor prognosis to benefit from postoperative adjuvant chemotherapy, despite absence of epidermal growth factor receptor mutations.

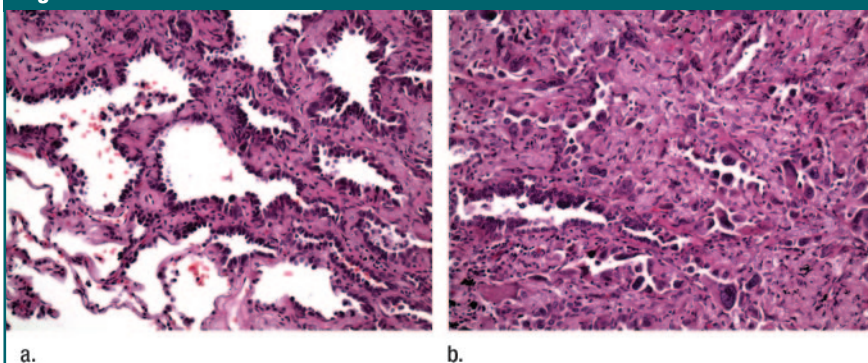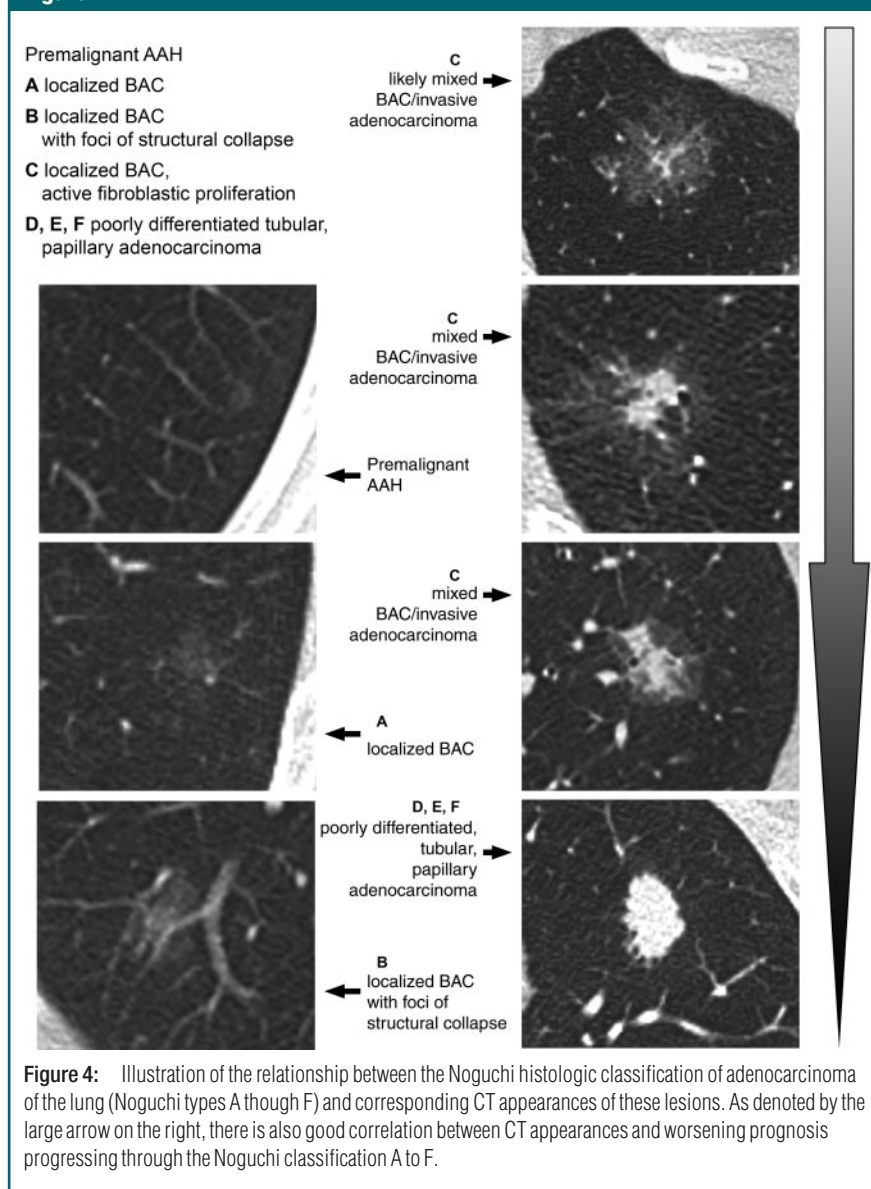Given these findings, it is not surpris-

Figure 3

a.   b.

Figure 3: Photomicrographs demonstrate mixed subtype adenocarcinoma. **(a)** BAC component. A single layer of cuboidal to columnar atypical cells grows along alveolar wall without stromal invasion. (Hematoxylin–eosin stain; original magnification, ×200.) **(b)** Invasive acinar adenocarcinoma. Stromal invasion is associated with a substantial increase of nuclear atypia and fibroblastic proliferation. (Hematoxylin–eosin stain; original magnification, ×200.)

ing that all studies to date have shown good correlation between CT features and prognosis in patients with peripheral adenocarcinomas. Most important, it has been shown that the percentage of GGO within lesions at CT correlates with the BAC (lepidic) component of the lesions in patients with histologically proved adenocarcinomas (18,20,24,33,34).

In the largest study to date evaluating the relationship between CT findings and prognosis, Vazquez et al (35) evaluated 338 patients with a diagnosis of adenocarcinoma in a low-dose CT screening program and showed that the proportion of BAC component within adenocarcinomas represented a positive prognostic factor and correlated with the proportion of GGO at CT. In keeping with prior reports, as the percentage of BAC histologically decreased from 100% to 0%, the proportion of GGO at CT similarly decreased, while the number of cases showing pleural, angiolymphatic, and bronchial invasion proportionately increased (35). They further reported that the 10-year Kaplan-Meier lung cancer-specific survival rate was 100% for patients with lesions that proved to have 90%–99% BAC component (similar to survival in patients with 100%). Patients with lesions with less than 90% BAC component had a poorer rate of survival (95%), but still better than those without a BAC component (90%).

The prognostic significance of the high percentage of BAC components in these lesions raises the question of the need for a new subclassification of adenocarcinoma, denominated "minimally invasive BAC" or "BAC with minimal invasion," as a separate category from mixed type adenocarcinoma with BAC features. On the basis of these data, some have recommended that adenocarcinomas with greater than 90% BAC component should be considered minimally invasive (35). Alternatively, it has also been suggested that lesions confirmed as pure BAC should be reclassified as adenocarcinoma in situ. Although suggestive, to date, proposed new subclassifications of these lesions have not yet been incorporated into the World Health Organization classification. It should be also noted that current staging TNM criteria for lung cancer does not take into account the above-discussed

Figure 4

Premalignant AAH
A localized BAC
B localized BAC with foci of structural collapse
C localized BAC, active fibroblastic proliferation
D, E, F poorly differentiated tubular, papillary adenocarcinoma

Figure 4: Illustration of the relationship between the Noguchi histologic classification of adenocarcinoma of the lung (Noguchi types A though F) and corresponding CT appearances of these lesions. As denoted by the large arrow on the right, there is also good correlation between CT appearances and worsening prognosis progressing through the Noguchi classification A to F.

CT and/or histologic characteristics of BAC and mixed subtype adenocarcinoma with BAC features. To date, both these lesions are similarly staged as T1, although the newly proposed staging system for non–small cell lung cancer does discriminate between lesions smaller than 2 cm and those between 2 and 3 cm in size (36).

Benign versus Malignant Subsolid Nodules: CT Evaluation

Given the close correlation between pathologic and CT findings in patients

with documented peripheral adenocarcinomas, the sensitivity and specificity of subsolid nodules identified at CT has also been evaluated, albeit most extensively in low-dose screening studies. To date, although most studies have confirmed close, although imperfect, correlation between the spectrum of adenocarcinomas and CT appearances, benign conditions, including organizing pneumonia, focal fibrosis, and focal inflammation, may also present as subsolid nodules (Fig 8) (9,37,38). Unfortunately, the value of CT in distinguishing benign from malignant

subsolid nodules, to date, has been reported to vary considerably (2,37–39).

As reported by Henschke et al (2), in a population of high-risk individuals screened with low-dose CT, while the rate of malignancy proved greater for part-solid (63%) than nonsolid (pure GGO) (18%) nodules, only 34% of subsolid nodules proved to be malignant compared with 7% for solid nodules. Similar findings have been reported by Kim et al (38), who retrospectively found in a nonscreened population that while 81% of persistent nonsolid nodules proved to be either AAH, BAC, or adenocarcinoma with BAC features, the remaining 19% proved histologically to represent either organizing pneumonia or nonspecific fibrosis (Fig 9). More disturbingly, in this study, there were no differences between benign and malignant lesions when assessed by shape, marginal characteristics, or the presence of pleural tags. Polygonal shape, nodule lobulation, or presence of irregular margins or spiculation was found in both malignant and benign lesions. Irregular margins, in particular, proved nondiagnostic, caused by interstitial fibrosis or infiltrative tumor growth in malignant lesions and granulation tissue in benign lesions, respectively.

In distinction, Lee et al (37), in a recent study evaluating 80 subsolid nodules (47 malignant and 33 benign), showed that CT predictors of malignancy for GGOs included size greater than 8 mm ($P = .04$) and lobulated border ($P = .01$), with lobulation associated with higher risk of malignancy ($P = .02$) for part-solid nodules. Most important, in this study all pure GGOs measuring 4 mm or less proved benign.

Interestingly, while not all subsolid nodules prove to be malignant, they rarely represent metastases, even in patients with documented extrathoracic tumors. In one study of 59 pathologically proved GGOs in 34 patients with a history of extrapulmonary malignancy, althought 28 (82.4%) patients proved to have lesions (including 24 adenocarcinomas, 16 BACs, 14 AAHs, four focal fibrotic foci, and one inflammatory nodule), there were no cases of metastases despite the fact that primary sites included adenocarcinomas of the breast, stomach, and colon (40).

Current Concepts in the Diagnosis and Management of Subsolid Nodules

Despite close correlation between CT findings and the spectrum of peripheral adenocarcinoma, the diagnosis and management of these lesions remain problematic given that not all subsolid nodules (and in particular lesions with pure GGO) prove to be malignant. Given limitations in sensitivity and specificity described above, alternate approaches to diagnosis and management necessarily have been investigated, including follow-up surveillance CT, alternate imaging studies that include positron emission tomography (PET) and/or combined PET/CT, and biopsy.

Correlation between the Noguchi Classification of Adenocarcinoma and World Health Organization 2004 Classifications and CT Findings

Noguchi Type	World Health Organization 2004	CT Features
. . .	AAH	GGO
A, Localized BAC	BAC (mucinous, nonmucinous and mixed mucinous and nonmucinous or indeterminate)	GGO
B, Localized BAC with alveolar collapse	BAC (mucinous, nonmucinous and mixed mucinous and nonmucinous or indeterminate)	GGO with possible solid component
C, Localized BAC with active fibroblastic proliferation	Adenocarcinoma, mixed subtype (with BAC component	Part-solid nodule with increase in solid component or solid nodule
D, Poorly differentiated	Solid adenocarcinoma with mucin	Part-solid nodule with greater increase in solid component or solid nodule
E, Tubular	Acinar adenocarcinoma	Part-solid nodule with greater increase in solid component or solid nodule
F, Papillary	Papillary adenocarcinoma	Part-solid nodule with greater increase in solid component or solid nodule

Note.—Adapted, with permission, from reference 9.

Figure 5

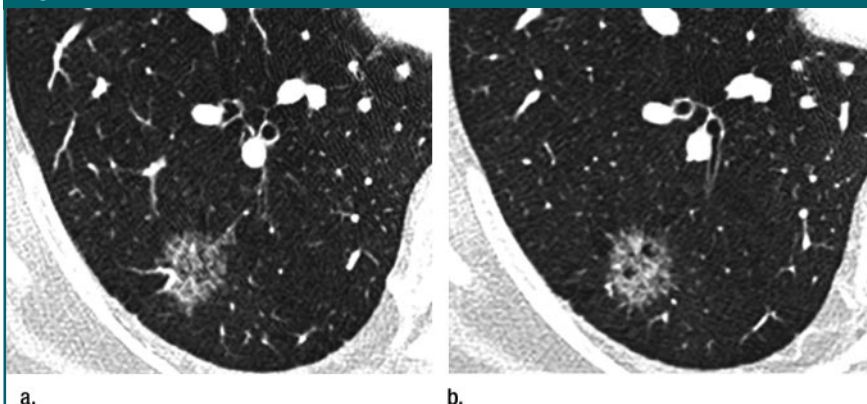a.   b.

Figure 5:   CT scans (1-mm section) of BAC (Noguchi type B lesion), heterogeneous GGO, show a nodule with GGO with **(a)** superimposed reticulation and **(b)** air bronchiolograms.

Growth Rate of Small Peripheral Adenocarcinomas in Low-Dose CT Screening for Lung Cancer

The mean doubling time of adenocarcinomas is longer than that of other tumor cell types, as shown in previous chest radiographic studies (41). A similar pattern has been identified with CT (Figs 10, 11) (39,42). In one study (39) of peripheral lung cancers identified at low-dose screening CT, when stratified according to tumor histologic type, the volume doubling time was higher for the spectrum of adenocarcinomas (988 days ± 470 for AAH, 567 days ± 168 for BAC, and 384 days ± 212 for mixed subtype adenocarcinoma with BAC features) compared with peripheral squamous cell carcinomas (122 days ± 68), importantly emphasizing that subsolid nodules tend to present considerably slower growth rates compared with solid lesions (39). The clear implication of these data is that the previous concept that lack of growth over a 2-year follow-up indicates a benign etiology does not apply for subsolid nodules.

Methods for Measuring Interval Change in the Appearance of Focal Nodules

By allowing for the slower growth rates of subsolid nodules, in particular, emphasis has been placed on means for obtaining accurate measurements at follow-up studies. Unfortunately, the accuracy of measurements of small lung nodules, in particular, is subject to high interobserver and intraobserver variability (43,44). Although three-dimensional volume measurements have been advocated by some, especially for evaluation of solid nodules, to date, there are less compelling data supporting the use of this approach for subsolid nodules (Fig 12) (45–48).

A simple change in the attenuation of lesions in itself may also be indicative of substantial interval change, making reliance on either unidimensional or bidimensional measurements potentially still less meaningful (Figs 13, 14) (49). Furthermore, as much as 5%–10% of
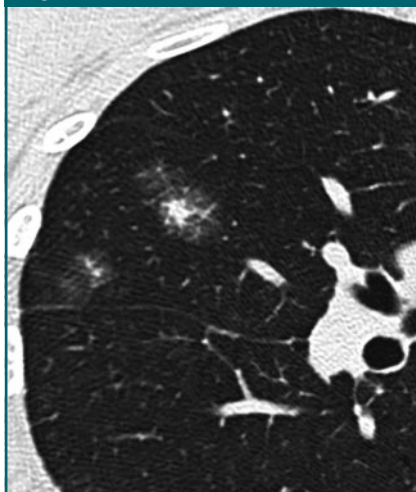
Figure 6

Figure 6: CT scan of mixed subtype adenocarcinoma with BAC component. Retrospective target reconstruction, 1-mm section, shows two part-solid nodules in the middle lobe with a central solid component and a ground-glass halo, which typically corresponds to Noguchi type C adenocarcinoma. (Reprinted, with permission, from reference 23.)

Figure 7

Figure 7: CT scan (1-mm section) of mixed subtype adenocarcinoma with BAC component (Noguchi type C lesion) shows a nodule with pure GGO, demonstrating that although nonsolid nodules are likely to represent AAH or BAC, an invasive component may rarely be present as in this case.
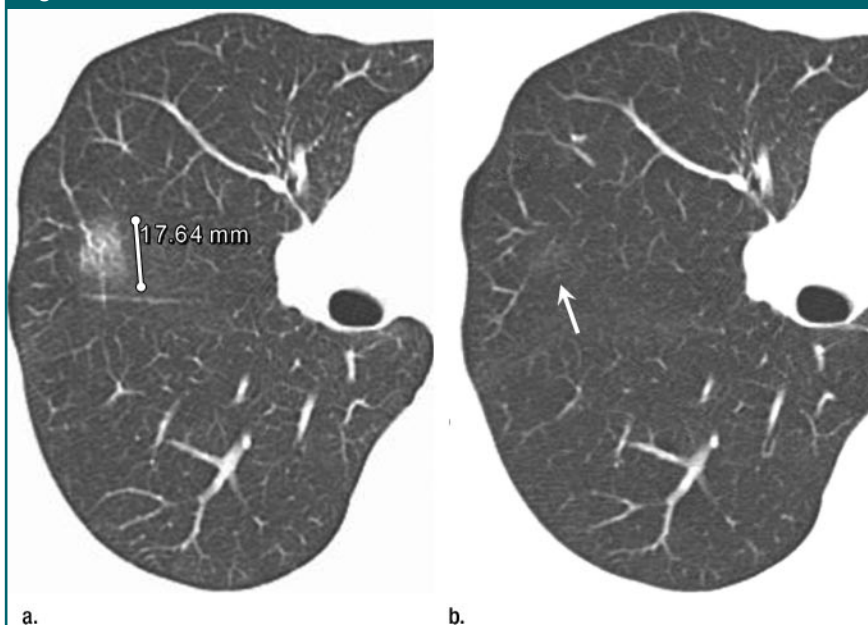
Figure 8

a.   b.

Figure 8: Focal inflammation mimicking adenocarcinoma. **(a)** Magnified 1-mm CT section through the right upper lobe shows nodules with GGO initially diagnosed as probable BAC. **(b)** Follow-up CT scan obtained 3 months later shows near complete resolution of the lesion (arrow), now presumed to represent focal nonspecific inflammation. (Reprinted, with permission, from reference 23.)

small malignant nodules may actually appear smaller with short-term follow-up intervals (50–52).

In an attempt to improve accuracy, Kakinuma et al (53) compared four methods for measuring GGOs: lesion length, a modified measurement of length that takes into account the length of a solid component, lesion area and its vanishing ratio, and the percentage of a lesion's area that is not seen at thin-section CT when comparing images reconstructed with mediastinal versus lung window settings. Of these, the vanishing ratio method, although subjective, proved the most accurate predictor of 5-year relapse-free survival (53). Although the advantage of such an approach seems logical on the basis of enhanced visualization of the solid component of lesions (Fig 15), this technique requires further validation prior to routine acceptance.

Regardless of approach, optimal evaluation of subsolid nodules, especially lesions with GGO, requires that appropriate CT technique be used. This includes most importantly the use of thin (1–3-mm) sections (54), as well as appropriate exposure factors (55). Given the likelihood of performing numerous follow-up CT studies, especially for smaller lesions, all effort should be made to minimize radiation exposure (56,57).

Role of PET

The important role of PET in the diagnosis and management of lung cancer is well established. For lesions as small as 8–10 mm in size, fluorine 18 fluorodeoxyglucose (FDG) PET is accurate in differentiating benign from malignant lesions, with an overall sensitivity, specificity, and accuracy of 96%, 88%, and 94%, respectively (58). FDG PET, however, has a lower sensitivity for small (<10 mm) or slow-growing lesions, such as carcinoid tumors and BAC (58–64). In a recent study, Tsunezuka et al (62) correlated the effectiveness of FDG PET to characterize adenocarcinomas (≤2 cm) with Noguchi classification and found that the false-negative rate for type A lesions was 100%, that for type B lesions was 80%, and that for type C lesions was 47%, while the true-positive rate for types D, E, and F lesions was 67%, 100%, and 86%, respectively (Fig 16). Similar results have been reported by Yap and colleagues (64).

It has been suggested that characteristic lower FDG uptake in BACs, when associated with CT findings that include nodule attenuation and size, can be of value in differentiating this tumor from mixed subtype adenocarcinomas with BAC features (65). Moreover, PET has been shown to also correlate with prognosis. Malignant nodules that have low FDG uptake are more likely to have an indolent nature and lack intratumoral lymphatic vessel invasion and lymph node metastasis (66), while high FDG uptake in an adenocarcinoma correlates with poorer survival (67). Despite these data, the role of FDG PET imaging for assessing predominantly lesions with GGO remains to be established.

Role of Transbronchial and Transthoracic Needle Biopsy for Diagnosis of BAC

Since a substantial percentage of subsolid nodules prove to be benign, it is reasonable to question the role of transbronchial needle aspiration biopsy to establish a diagnosis. A major potential limitation to transbronchial needle aspiration biopsy is the fact that accurate differentiation between AAH, BAC, and mixed type adenocar-
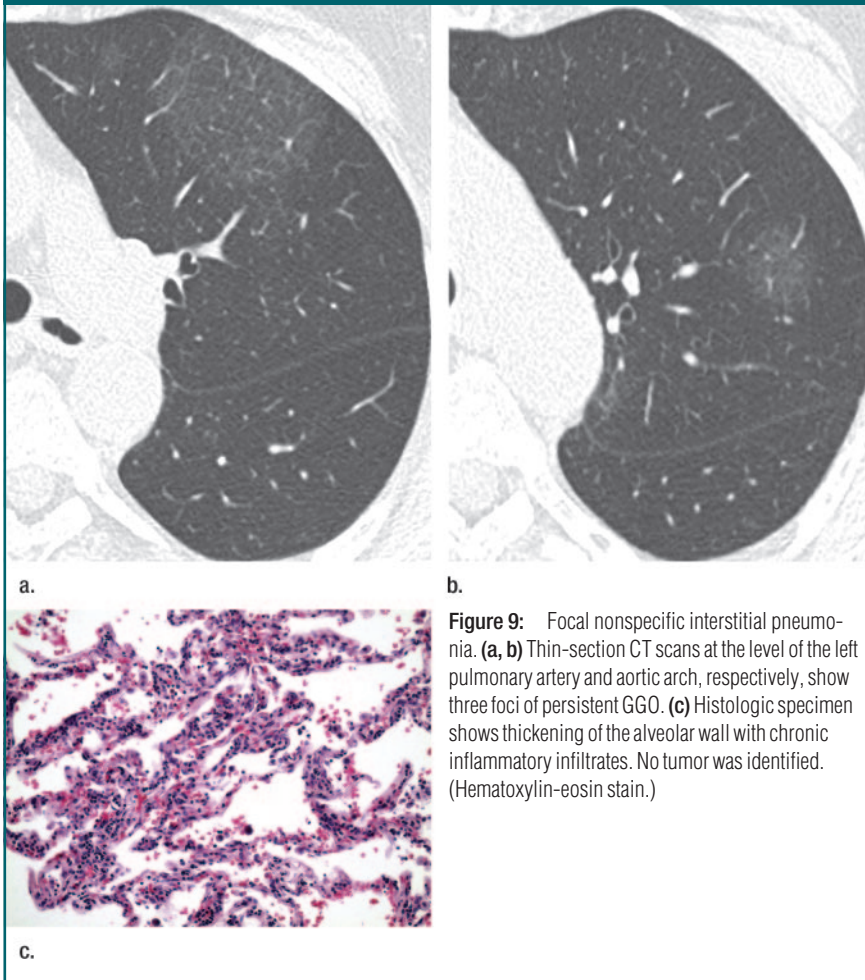
Figure 9

Figure 9: Focal nonspecific interstitial pneumonia. **(a, b)** Thin-section CT scans at the level of the left pulmonary artery and aortic arch, respectively, show three foci of persistent GGO. **(c)** Histologic specimen shows thickening of the alveolar wall with chronic inflammatory infiltrates. No tumor was identified. (Hematoxylin-eosin stain.)

cinomas with bronchioloalveolar components may not be feasible on the basis of limited cytologic or even histologic sampling.

The diagnostic yield of CT-guided fine-needle aspiration biopsy for subsolid nodules has been evaluated by Shimizu et al (68), who found a diagnostic yield in ground glass– dominant lesions (GGO ratio > 50%) and solid-dominant lesions (GGO ratio < 50%) of 51.2% and 75.6%, respectively. The overall diagnostic yield of CT-guided fine-needle aspiration biopsy, however, was only 64.6%, while for lesions smaller than 10 mm with predominantly ground-glass appearance the diagnostic yield was as low as 35.2%.

In an attempt to improve diagnostic accuracy, it has been suggested that subsolid nodules should preferentially be evaluated with core needle biopsy. Kim et al (69) evaluated the accuracy of CT-guided core biopsy for the diagnosis of subsolid lesions and found that the overall concordance rate between core and surgical biopsies in malignant and premalignant lesions was 73%. However, in 28% of cases diagnosed at surgical resection as mixed subtype adenocarcinoma with BAC features, the core biopsy failed to identify the area of invasion, incorrectly diagnosing the lesion as BAC. The authors concluded that, given the requirement for BAC to show pure lepidic growth without invasion, correlation with thin-section CT images is necessary and that complete surgical removed is necessary to exclude invasion before a final diagnosis of BAC can be determined (69).

In fact, difficulty in establishing a definitive pathologic diagnosis even in cases for which surgical biopsies are available has recently been reported. In a review of histologic diagnoses reevaluated by a panel of expert pathologists in a population of patients accrued in a low-dose CT lung cancer screening study, 50 of 59 lesions initially diagnosed in outside institutions as BACs were revised to invasive adenocarcinoma, while an additional 10 cases, all smaller than 5 mm in size, initially diagnosed as AAH in patients
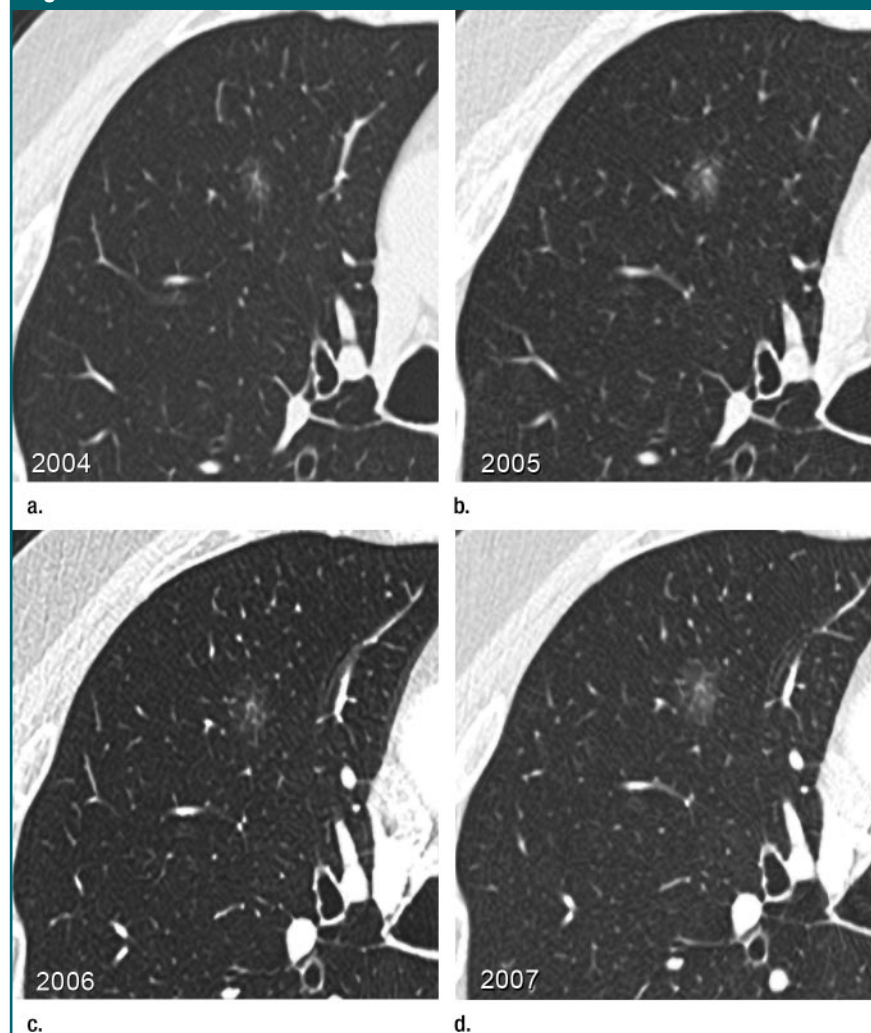
Figure 10

Figure 10: BAC. Sequential magnified 1-mm CT sections through the right upper lobe show minimal increase in size of a nodule with GGO over a 3-year period. The central area of higher attenuation represents a vessel bifurcation and not a solid component, which was better characterized on sequential images.

with established lung cancers were reinterpreted as nine BACs and one invasive adenocarcinoma (15).

On the basis of these data, it is concluded that transbronchial needle aspiration biopsy ideally should only be performed in patients with subsolid nodules at CT who are either nonsurgical candidates, surgical candidates for whom proof of malignancy is still considered necessary, or who present with multifocal disease (70). In these cases, correlation of transbronchial or transthoracic needle biopsy with CT results can be used for a presumptive diagnosis.

Surgical Resection of Small Peripheral Adenocarcinomas

In light of recent data documenting markedly improved 5-year survival of patients with subsolid nodules, in particular BAC (77–74), despite previous consensus for the need to perform lobectomy for stage 1 lung cancer (75), the potential role of limited surgical resections, including partial wedge resections and segmentectomies, has come under renewed scrutiny (71–74,76–79).

Currently, most studies have focused on limited surgical resections for patients with BAC (71,72,74,78),

while the value of limited resection for minimally invasive adenocarcinoma (24,74,76) and part-solid nodules with ground-glass component greater than 50% have also been reported (24,76). In these studies, cases in which radical segmentectomies with hilar and mediastinal lymph node dissections or sampling only were performed, no postoperative recurrences were identified, which is consistent with the high curability rate of these cancers.
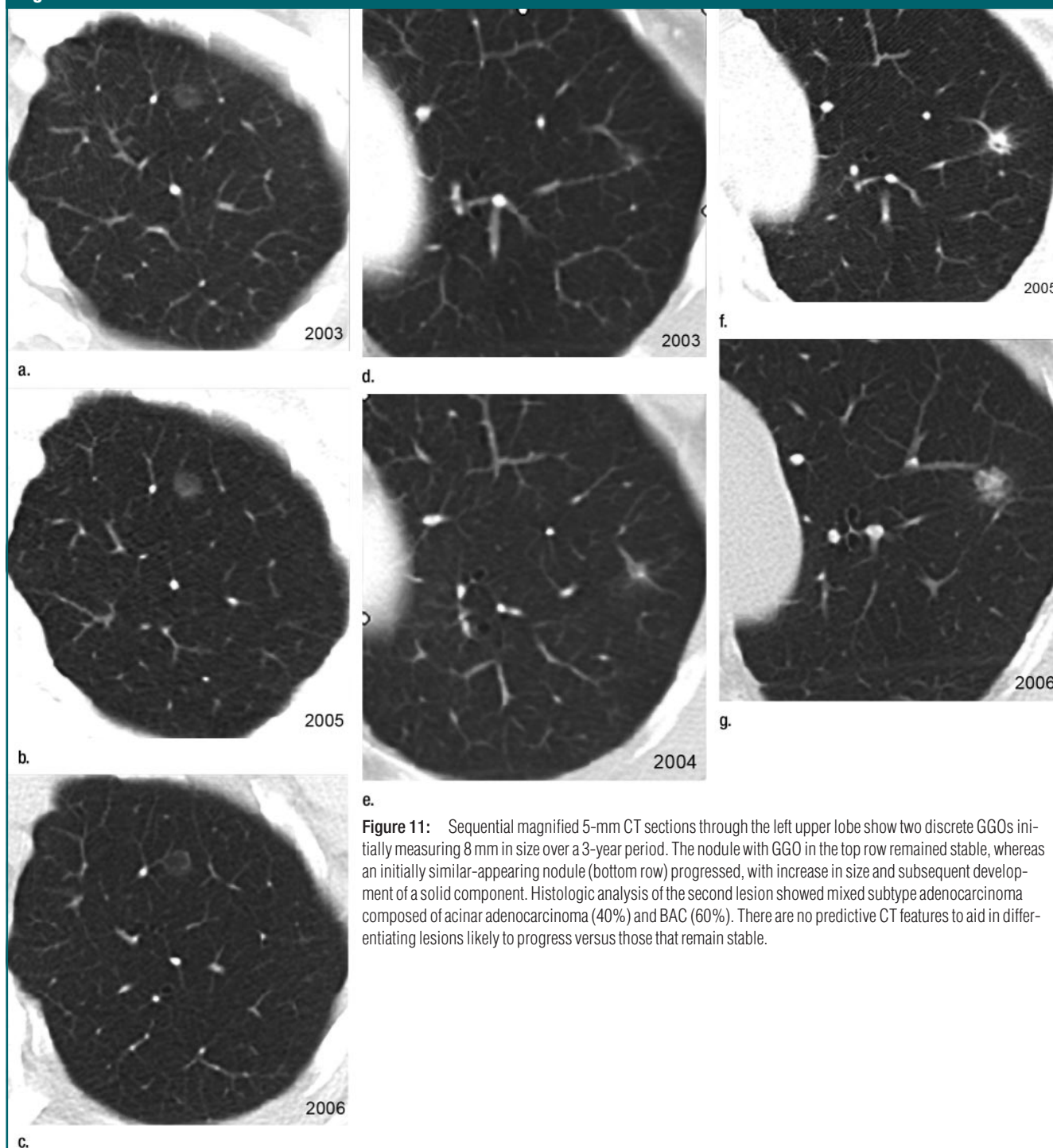
Figure 11

Figure 11: Sequential magnified 5-mm CT sections through the left upper lobe show two discrete GGOs initially measuring 8 mm in size over a 3-year period. The nodule with GGO in the top row remained stable, whereas an initially similar-appearing nodule (bottom row) progressed, with increase in size and subsequent development of a solid component. Histologic analysis of the second lesion showed mixed subtype adenocarcinoma composed of acinar adenocarcinoma (40%) and BAC (60%). There are no predictive CT features to aid in differentiating lesions likely to progress versus those that remain stable.

As documented in a recent report by Vazquez et al (35), contrary to traditional staging predictions, cases of multiple, node-negative adenocarcinoma proved to have the same excellent prognosis as solitary node-negative cases. In this study (35), the 10-year Kaplan-Meier survival rate of 213 patients with pathologic node-negative solitary lung cancer was 97% (95% confidence interval: 95%, 100%) versus 100% for 44 patients with multiple node-negative malignancy, with no significant difference between these two rates ($P = .29$). These data suggests that most of the small, node-negative multiple adenocarcinomas currently identified at CT most likely represent multiple primary cancers rather than intrapulmonary metastasis.

Mun et al (73) have further confirmed the benefits of limited resections for Noguchi types A to C lesions, including a 70.3% overall 5-year disease-free survival of patients with multifocal BAC. Similarly, Carreta et al (77) in a study of 26 patients with multiple primary adenocarcinomas of the lung and a total of 52 tumors found a favorable result with surgical treatment. Additionally, they reported that sublobar resections, when feasible, provided adequate oncologic management (77).

Current Status and Ongoing Controversies in the Management of Subsolid Lung Nodules

It is apparent from the preceding discussions that pulmonary nodule characterization and indications for therapy are undergoing profound changes as new clinical, radiologic, and pathologic data are reported. Although advanced technology, in particular multidetector CT, has provided important new insights, it is equally apparent that the same technology has created an entirely new set of problems requiring consideration.

Patients for Whom Follow-up Studies Are Prioritized in Place of Biopsy or Surgery

The optimal time and especially duration of follow-up imaging studies in patients with subsolid nodules remain to be determined (Fig 10). As noted above, especially for lesions with pure
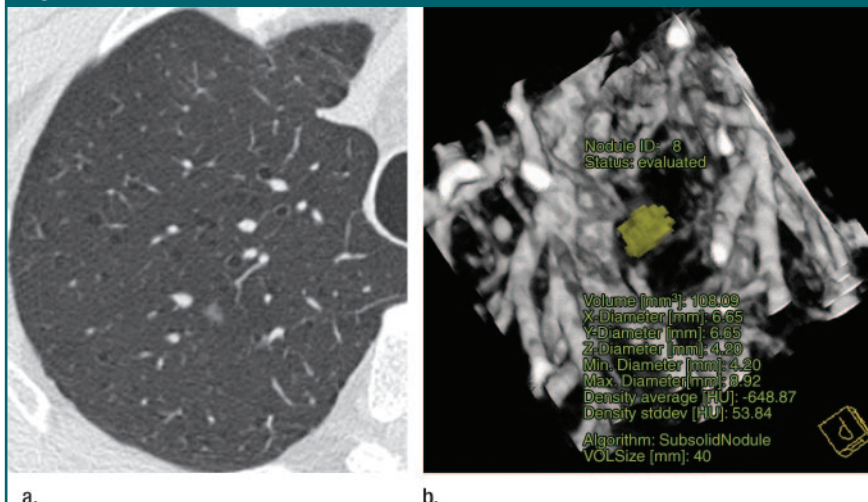

Figure 12

Figure 12: Automated three-dimensional segmentation. **(a)** Magnified 1-mm CT section through the right upper lobe shows a nodule with GGO with indistinct margin. **(b)** Corresponding three-dimensional segmentation provides automated estimation of its volume and cross-sectional dimensions in the x, y, and z planes, as well as minimum and maximum diameters measured in off-axial planes.
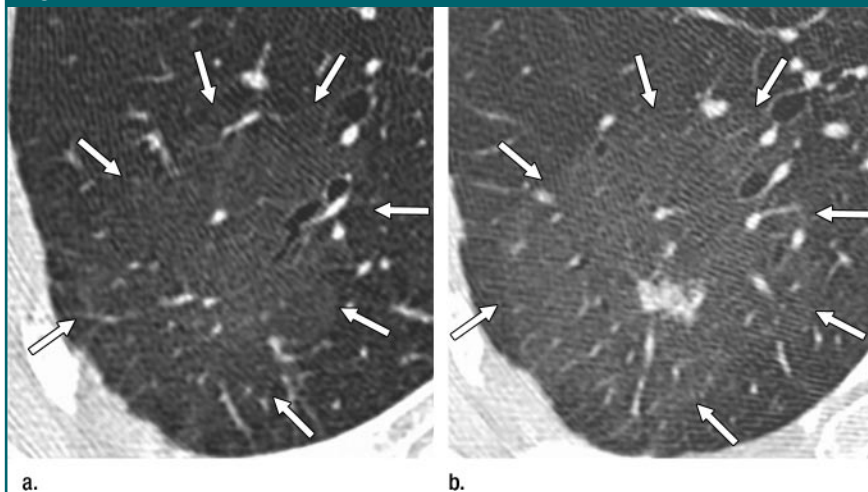

Figure 13

Figure 13: Mixed subtype adenocarcinoma, progression of GGO to a nodule with mixed solid component and GGO. **(a)** Magnified 1-mm CT section shows a discrete GGO (arrows). **(b)** Follow-up CT scan obtained 1 year later shows clear progression of the disease, with the development of a central solid component, although there is no appreciable enlargement of the lesion (arrows).

GGO, traditional 2-year follow-up periods are insufficient to safely diagnose benign disease.

The best method for measuring lesions in cases in which follow-up imaging studies are performed also requires continued evaluation. The need for improved methods to accurately measure lesions that are otherwise poorly or irregularly marginated, in particular, remains a clear priority (43,45,46,48,53). Perhaps most important, the relationship between AAH, BAC, and invasive adenocarcinoma requires further clarification. Determining how often and how rap-

idly lesions with pure GGO enlarge or increase in attenuation at present remains problematic when based solely on CT morphologic grounds. It should be noted that to date only limited data are available that document the nature of disease progression in patients with subsolid nodules (21,22). In one study (22) in which follow-up CT studies were used to evaluate 48 subsolid lesions diagnosed as either AAH or Noguchi types A-C adenocarcinomas, of those initially recognized as nodules with pure GGO (56%), 75% subsequently demonstrated an increase in size (Fig 10), with solid components first appearing in 17% (Fig 13) and subsequently increasing in size in 23% (Fig 14). While these data support the concept proposed by Noguchi et al (12) that there is a stepwise progression of replacement types A to C lesions, these authors failed to provide any insight into any predictive CT features to aid in differentiating lesions likely to progress (Fig 11).

Patients with Multiple Subsolid Nodules

While the distribution of histologic subtypes differs from that seen in solitary nodules, the implications for patient treatment remain unclear. For example, treatment of patients with multiple tiny (< 5 mm) GGOs presumably will differ from treatment of patients with multiple, variable-sized lesions, especially those with one or a few dominant lesions, including those larger than 10 mm (Fig 17) or those that are part-solid in appearance (Fig 18). In the latter case, the value of limited surgical resections in patients with multiple lesions, one or a few of which prove to be dominant either by size or attenuation, remains to be determined.

Is There Overdiagnosis of Lung Cancer in Patients with Subsolid Nodules?

Although a detailed evaluation of this complex issue is outside the scope of the present report, this question does bear mentioning given the current intense interest toward the potential of low-dose CT lung cancer screening to decrease lung cancer mortality (15,80,81). Preliminary reports do seem to indicate that in select cases identification of small subsolid lesions at CT may in fact lead to overdiagnosis and unnecessary treatment (82). Lindell et al (52), in one recent study, for example, evaluated 61 lung cancers and found 27% of them had a mean volume doubling time longer than 400 days, meeting criteria for overdiagnosis according to those previously proposed (83). Furthermore, in this same study, the mean volume doubling time was longer in women, raising concern of even higher likelihood of overdiagnosis in this population (84).

Additional insight into the likelihood of overdiagnosis in screened population may be inferred from a recent report by
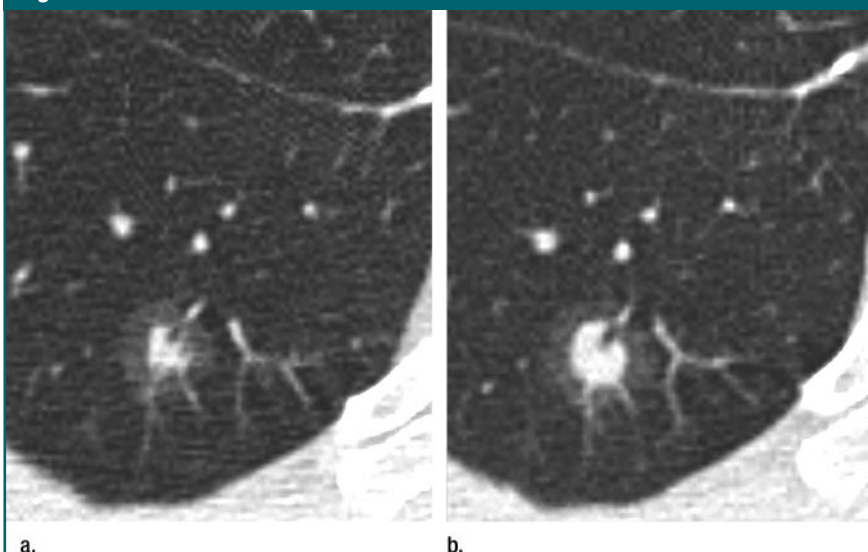
Figure 14

a.   b.

Figure 14: Mixed subtype adenocarcinoma. **(a)** Magnified 1-mm CT section through the left lower lobe shows a nodule with mixed solid component and GGO. **(b)** Follow-up CT scan obtained 6 months later shows increase in the extent of the solid component within the nodule.

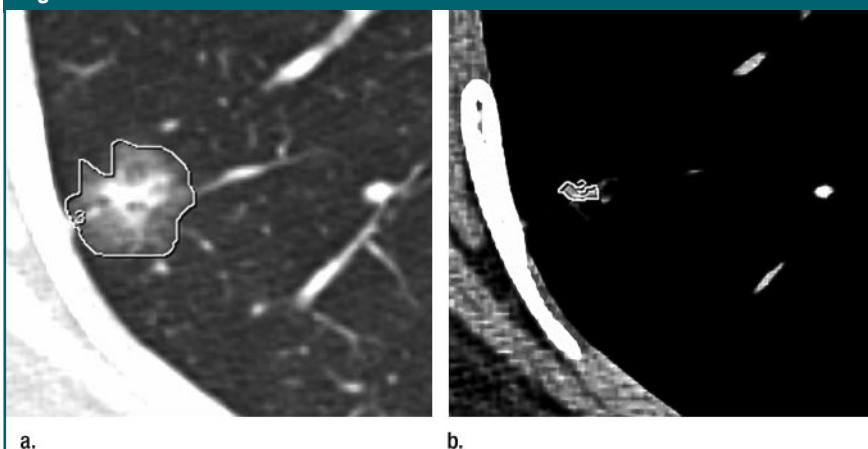**Figure 15**

a.   b.

Figure 15: Thin-section CT images of nodule with mixed solid component and GGO. The vanishing ratio represents the percentage of the area of the lesion that is not seen at thin-section CT when comparing images reconstructed with **(a)** lung versus **(b)** mediastinal window settings. The mediastinal window setting is used to enhance visualization of the delimitation of the solid component.

Carter et al (15), in which histologically proved lesions identified at 174 baseline (prevalence) studies were compared with those from 37 annual (incidence) screening studies. Of the baseline cancers, 142 (82%) of 174 proved to be adenocarcinomas, of which 84 (60%) proved to be subsolid lesions, nine proved to be BACs, and 75 proved to be mixed type adenocarcinomas. Importantly, of these 84 subsolid lesions, only 14 (17%) proved invasive at resection. In distinction, of 37 follow-up (incidence) cancers identified, only six (16%) proved to be subsolid lesions versus 60% at baseline screenings (15). These data, while still inconclusive, are consistent with the notion of overdiagnosis occurring in at least some percentage of screening-identified lesions.

It is worth emphasizing that these data leave unanswered the question of the clinical significance of a histologic diagnosis of "minimal invasion," an issue still unresolved with important implications for clinical management. It may be anticipated that better understanding of the natural history of adenocarcinomas that allows differentiation between indolent tumors from more aggressive lesions will likely have to await the development of ancillary measures, including the use of biologic markers (84).

Suggested Guidelines in the Management of Subsolid Nodules

Incidentally identified, isolated pure GGOs smaller than 5 mm in size represent foci of AAH sufficiently often to obviate routine follow-up CT studies, especially in the elderly. Although it is acknowledged that some of these lesions may prove to be BAC, the extreme rarity of invasive adenocarcinomas in this subgroup coupled with their extremely prolonged doubling times suggest that there is no reason to undergo either the added expense or radiation exposure necessary to follow these lesions presumably over prolonged time intervals measured in years. An exception is patients enrolled in low-dose lung cancer screening programs for which follow-up imaging is presumably dictated by protocol.

Given that the uncertainty regarding
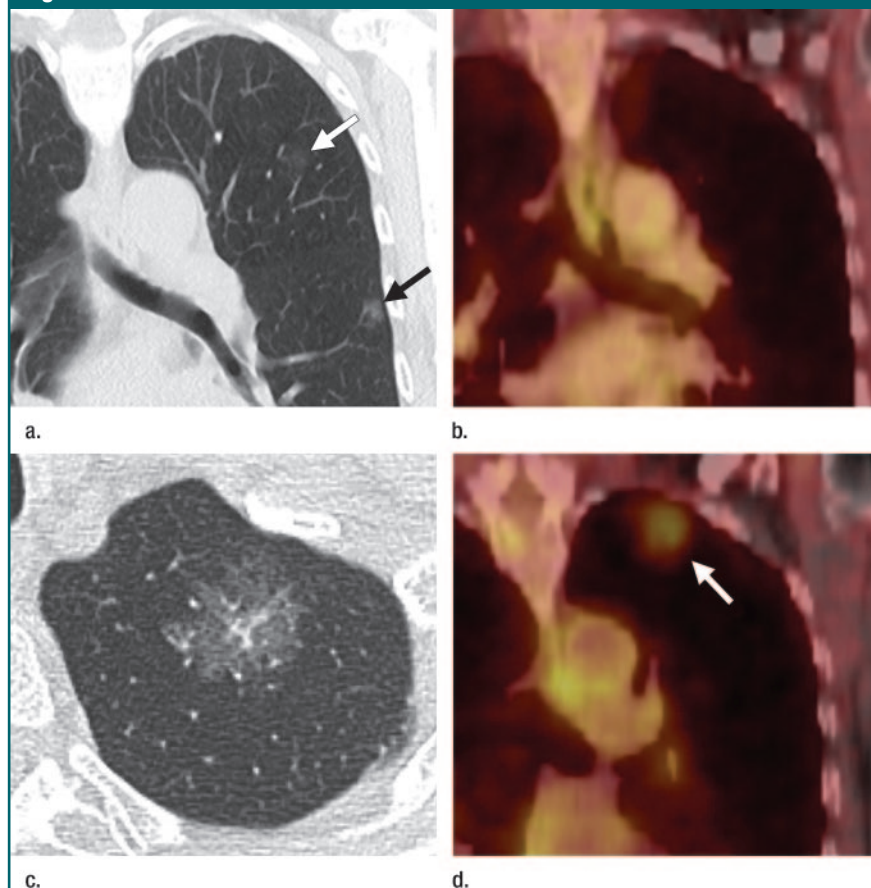

Figure 16

Figure 16: Subsolid nodule characterization with PET/CT. **(a)** Coronal 5-mm CT section shows multicentric BAC characterized by GGOs in the left upper and lower lobes (arrows), corresponding to Noguchi types A and B, respectively. **(b)** Correlated coronal PET image shows no FDG uptake by the lesions (false-negative study). **(c)** Axial magnified 1-mm CT section in another patient shows mixed subtype adenocarcinoma (Noguchi type C lesion), characterized by mixed solid and ground-glass appearance. **(d)** Correlated coronal PET image shows FDG uptake (arrow) by the lesion in the left upper lobe (maximum standardized uptake value, 3.4).

the above issues will likely persist for the foreseeable future, by using currently available data, the following interim guidelines are proposed. These do not differentiate between low- and high-risk group as per Fleischner criteria (85) due to the increased incidence of adenocarcinomas in younger and nonsmoking patients. It cannot be overemphasized that these guidelines need to be interpreted in the light of individual clinical history.

Lesions Smaller than 10 mm with Pure GGO

Isolated lesions smaller than 5 mm in size with pure GGO represent foci of AAH sufficiently often to obviate follow-up CT studies.

Conservative management of nodules between 5 and 10 mm in size with pure GGO requires at least an initial follow-up examination in 3–6 months to document that lesions have not resolved spontaneously (or following antibiotic therapy). Although a small percentage of these lesions will prove to be invasive adenocarcinomas, the role of surgical biopsy in these cases remains problematic with appropriate management, necessitating case by case evaluation. For most of these lesions, continued long-term follow-up is likely preferable to surgical resection.

When opted for, follow-up surveillance should extend for more than 2 years. As the optimal duration of fol-

low-up of lesions with pure GGO has yet to be determined, at least three consecutive annual studies is a minimum requirement to document stability. The need for further follow-up examinations remains speculative: While the number of lesions that enlarge or increase in attenuation later than 3 years is small, a sufficient number evolve to justify extended surveillance. In our experience, it was for as long as 5 years, although it cannot be overemphasized that the risk of subsequent development of cancer clearly needs to be balanced against the risks of unnecessary radiation exposure and especially surgical intervention (86).

Accurate assessment of interval change is best accomplished by comparing thin-section CT scans, allowing as precise comparison as possible to minimize both inter- and intraobserver variability in measurements, as well as close monitoring of any change in the attenuation of lesions, as either change should be interpreted as indicative of possible malignancy, in most cases necessitating surgical resection.

PET or PET/CT scans are of questionable diagnostic value or may even be misleading in the majority of cases of lesions smaller than 1 cm in diameter and should not be routinely obtained, especially given the small likelihood of associated metastatic disease rendering the potential use of PET for staging less useful.

Transbronchial aspiration should be discouraged as unlikely to provide sufficient data to either accurately assess malignant potential or establish a benign diagnosis. Instead, core needle biopsy should be preferentially performed, especially in cases for which surgery is contraindicated and histologic evaluation is deemed necessary.

In all cases in which follow-up surveillance is undertaken, subsequent CT studies should be performed with the lowest possible exposure techniques to minimize radiation exposure in these patients. In our ex-
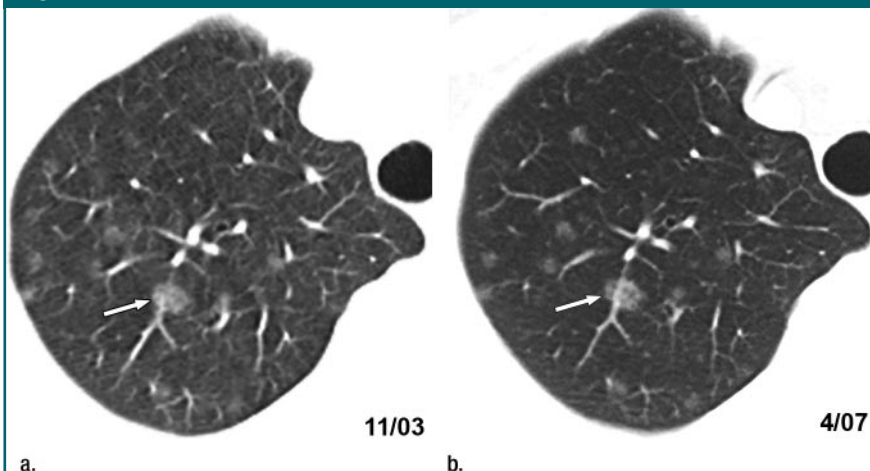
Figure 17

Figure 17:   Variable-sized subsolid nodules. **(a)** Magnified 1-mm CT section through the right upper lobe shows multiple small lesions with GGO and one dominant larger nodule with GGO (arrow). **(b)** CT scan at 4-year follow-up shows no substanital interval change (arrow) and the lesions were presumed to represent AAH and BAC (dominant lesion).
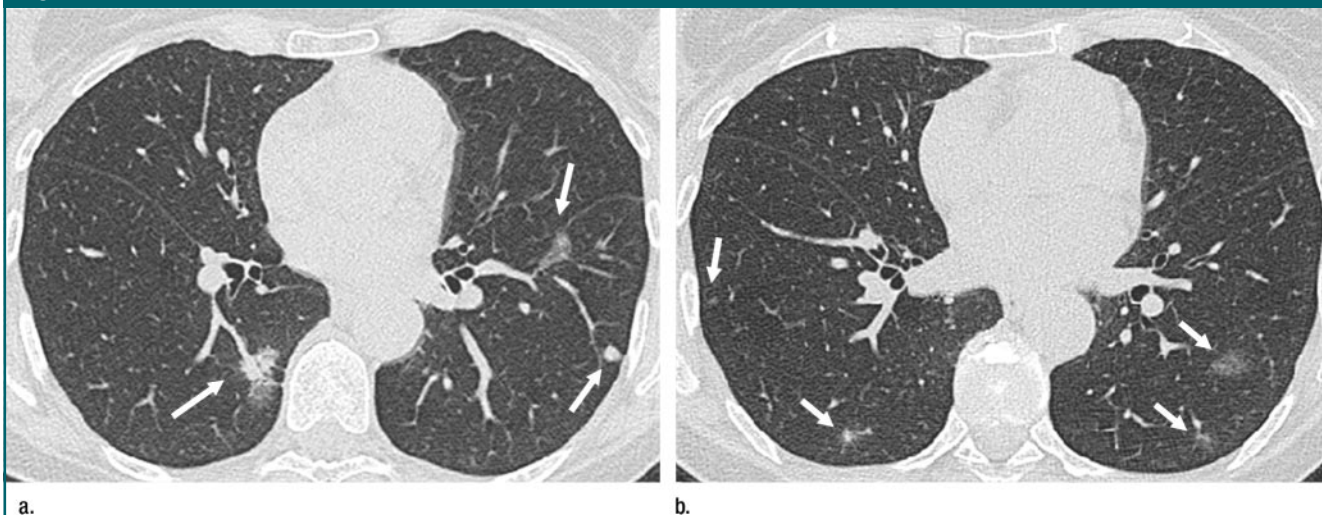
Figure 18

Figure 18:   Multiple subsolid nodules with variable size and appearance. **(a, b)** Sequential axial 1-mm CT sections through the mid thorax in the same patient show multiple subsolid pulmonary nodules differing in size and attenuation located in the superior segment of the right and left lower lobes (arrows), including nodules with mixed solid component and GGO, nodules with GGO, and a solid nodule. In such cases, selective limited resection of the dominant lesions may be acceptable, contrary to standard treatment of patients with multiple foci of BAC and/or adenocarcinoma.

perience, studies performed with as low as 80 mAs (depending on body habitus) are of sufficient quality to allow accurate follow-up assessment of these lesions.

Solitary Lesions 10 mm or Larger in Size with GGO

As a general rule, solitary lesions 10 mm or larger in size with pure GGO should be resected, provided that persistence or growth of the lesion is again established over at least a 3–6-month period. In this setting, indications for percutaneous needle biopsy are still limited as the likelihood of a definitive histologic diagnosis remains problematic given substantial sampling error. Similarly, indications for PET or PET/CT remain doubtful as PET-negative studies do not exclude the possibility of invasive adenocarcinoma, while these lesions are also still unlikely to be associated with distant metastases.

Lesions with Mixed Solid Component and GGO

Similar to solitary lesions 10 mm or larger in size with GGO, any lesion with mixed solid component and GGO, regardless of size, represents malignancy with sufficient likelihood to warrant further evaluation. The evaluation should include the timely performance of PET or preferably PET/CT, since there is a greater likelihood that these lesions represent invasive tumors for which preoperative staging and assessment of prognosis is warranted. Less clear is the role for transbronchial and/or transthoracic biopsy in these cases, given the limited value of accurate differentiation between BAC and invasive adenocarcinomas, especially for lesions with less than 50% solid components, and the likelihood that these lesions will be resected, regardless.

Multiple Subsolid Nodules

In cases of multiple lesions smaller than 5 mm with pure GGO, at least 1-year follow-up surveillance CT study should be performed on the premise that these patients may be at greater risk than the general population for developing cancer. However, continued long-term follow-up should not be considered necessary.

In general, follow-up CT surveillance is to be preferred in cases in which multiple small (5–10-mm in size) lesions are

identified, as these most likely represent either multifocal AAH or in smokers, respiratory bronchiolitis.

In distinction, *(a)* surgical resection should be considered, especially in cases in which there are dominant lesions, defined as GGOs greater than 10 mm in size or lesions with mixed solid component and GGO; *(b)* PET or preferably PET/CT should be performed following a similar logic as outlined above for solitary lesions with mixed solid component and GGO; and *(c)* limited lung-sparing resections may be considered as an option to routine lobectomy given the likelihood that at least some of the remaining lesions will continue to grow.

In conclusion, new appreciation of the importance of subsolid nodules has led to the need for a reappraisal of the natural history of such lesions. While numerous controversial aspects remain, the main purpose of this report has been to set out interim guidelines based on best-guess estimates, the authors' extensive albeit anecdotal experience, and especially currently available published data. It cannot be overemphasized that the guidelines proposed in this review pertain to subsolid nodules only and are not intended to supplant guidelines regarding the management of solid nodules that have already been published both as a consensus statement of the Fleischner Society (85) and more recently by the American College of Chest Physicians (87).

It is anticipated that future developments based on multidisciplinary efforts will result in greater consensus regarding optimal CT classification of subsolid lesions and ultimately more definitive, evidence-based guidelines leading to more rigorous standardization and ultimately improved clinical treatment of patients with subsolid lung nodules.

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