Recent advances in technology, including the widespread availability of multidetector computed tomography (CT) scanners and emerging data in support of lung cancer screening, have broadened our understanding and awareness about small pulmonary nodules. In particular, knowledge of the subsolid nodule has grown as detection with CT has increased in conjunction with thin-section imaging.\(^1,2\) Subsolid nodules include both “pure” ground-glass (pGGN) and part-solid (PSN) lesions. Although these nodules may be inflammatory or infectious in etiology, a high association with the recently redefined pathologic spectrum of lung adenocarcinoma has been established, rendering subsolid nodules of heightened clinical importance.

In this review, we focus on the radiologic, clinical, and pathologic aspects primarily of solitary subsolid pulmonary nodules. Particular emphasis will be placed on the pathologic classification and correlative CT features of adenocarcinoma of the lung.\(^3\)

The capabilities of fluorodeoxyglucose positron emission tomography-CT (FDG PET-CT) and histologic sampling techniques, including CT-guided biopsy, endoscopic-guided biopsy, and surgical resection, are discussed. Finally, recently proposed management guidelines by the Fleischner Society and the American College of Chest Physicians (ACCP) are reviewed.\(^1,2\)

**DEFINITIONS AND TERMINOLOGY**

A lung nodule is technically defined as a rounded opacity that is smaller than 3 cm in diameter. Subsolid nodules are those containing at least some component of ground-glass attenuation. Subsolid nodules are further classified as either “pure ground glass” (pGGN) or “part solid” (PSN) in appearance. According to the Fleischner Society glossary of terms for thoracic imaging,\(^4\) a ground-glass opacity (GGO) is defined as “a hazy increased opacity of lung, with preservation of bronchial and vascular...
margins. It is caused by partial filling of airspaces, interstitial thickening (due to fluid, cells, and/or fibrosis), partial collapse of alveoli, increased capillary blood volume, or a combination of these, the common factor being the partial displacement of air." The term "pure GGN" refers to nodules of only ground-glass attenuation on CT, whereas the term "part-solid GGN" describes those that exhibit a combination of ground-glass and solid attenuation, which obscures the underlying lung architecture on CT. The term opacity can be used when the subsolid focal opacity is less round or very poorly defined from the adjacent parenchyma, although the delineation between nodule and opacity is challenging. In distinction, the term ground-glass "attenuation" should be applied to larger, less distinct areas of poorly defined areas of increased lung density through which normal lung structures may still be identified. It should be noted that although the term "CT halo sign" and its opposite, the "reverse halo sign" incorporate both solid and ground-glass elements, these lesions should be considered as separate and distinct entities and therefore are considered separately.

EPIDEMIOLOGY

Knowledge of the frequency of subsolid nodules has been gained primarily through screening CT studies. The frequency of subsolid nodules among all nodules has varied among reports. Henschke and colleagues\(^5\) reported that the frequency of subsolid nodules among all (233) nodules in the Early Lung Cancer Action Project (ELCAP) was 19%. Lung cancer screening studies in Korea\(^6\) and Ireland\(^7,8\) reported the frequency of subsolid nodules to be 6.3% of 4037 nodules and 7.7% of 168 nodules, respectively. Another study from Japan by Li and colleagues\(^9\) reported a 38% frequency of subsolid nodules. The NELSON study (Dutch-Belgian Randomized Lung Cancer Screening Trial) reported an incidence of 2.5% for “partially solid” and 3.5% for “nonsolid” nodules among the 2236 nodules that were detected.\(^10\)

ETIOLOGY

Subsolid nodules may be transient or persistent. Although a close association between subsolid nodules and the recently redefined spectrum of adenocarcinomas of the lung has been reported, a considerable percentage of subsolid nodules (both transient and persistent) will prove to be benign. Benign etiologies include infectious and inflammatory conditions, including organizing pneumonia, focal interstitial fibrosis, and hemorrhage. Malignant etiologies include the spectrum of adenocarcinoma and, rarely, pulmonary metastasis especially due to malignant melanoma.

Transient Subsolid Nodules

A substantial proportion of subsolid nodules are transient, ranging between 38% and 70%,\(^11-13\) resolving either spontaneously or after a course of antibiotics. Felix and colleagues\(^11\) reported that 43.8% of 75 pure GGOs in a lung cancer screening program disappeared on follow-up chest CT. Oh and colleagues\(^12\) reported 37.6% of 69 pGGNs and 48.7% of 117 mixed GGNs resolved. Lee and colleagues\(^13\) reported that and 69.8% of 126 subsolid nodules were transient. Oh and colleagues identified young patient age, blood eosinophilia, lesion multiplicity, polygonal shape, ill-defined borders, and a large degree of solid component as among the suggested clinical and CT features that predicted transient rather than persistent lesions.\(^11-13\) Felix and colleagues\(^11\) found that nodules that resolved were more often lobular GGOs, with mixed attenuation, and larger size than those that persisted. For this reason, follow-up thin-section CT imaging has been recommended to confirm the persistence or disappearance of subsolid nodules such as at 3 months (Fig. 1).\(^1\) Although antibiotics have been used before obtaining follow-up examinations,\(^14,15\) their use is not included in current management guidelines.\(^1,2,16\)

Although transient subsolid nodules are due to a variety of nonspecific infectious and inflammatory conditions, most often the precise etiology remains unknown. Interestingly, Aspergillus is one reported potential etiology for a transient subsolid nodule.\(^17\) Eosinophilia has been noted to occur with some frequency in patients with transient subsolid nodules, although, as reported by Oh and colleagues,\(^12\) short-term follow-up chest CT should be obtained for GGNs in the presence of high blood eosinophilic count, regardless of lesion size, to confirm clearance.

Other inflammatory etiologies resulting in transient subsolid nodules include antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, Kaposi sarcoma, and other fungal infections, more commonly multiple than solitary.\(^18\) Thoracic endometriosis related to ectopic endometrial tissue can also lead to focal hemorrhage,\(^19\) resulting in subsolid lesions.\(^19\)

Persistent Subsolid Nodules

The most common causes of persistent subsolid nodules are lesions that fall within the pathologic spectrum of lung adenocarcinoma.\(^5,20-23\) Less
common causes include pulmonary lymphoproliferative disorders, organizing pneumonia, and focal interstitial fibrosis. Subsolid lung nodules are an especially common presentation of adenocarcinomas in lung cancer screening studies. Henschke and colleagues, for example, reported that 34% of detected subsolid nodules (63% of PSNs and 18% of pGGNs) proved malignant, whereas only 7% of solid nodules proved malignant. Similarly, in a study of resected or tissue-confirmed persistent subsolid nodules by Kim and colleagues, 81% of the 53 persistent subsolid nodules turned out to be in the spectrum of premalignant and malignant lung adenocarcinomas, including 75% of cases representing bronchioloalveolar (or bronchoalveolar) carcinoma (BAC) (the preferred term at the time of the study) and 6% representing atypical adenomatous hyperplasia (AAH). On the other hand, 19% of the nodules proved to be benign, representing organizing pneumonia or focal interstitial fibrosis.

Lung adenocarcinoma: new revised histologic classification

The most common cause of a persistent subsolid nodule is lung adenocarcinoma, and a close correlation between the CT appearance and pathologic findings is now well established. Adenocarcinoma is now the most common histologic subtype occurring in both smokers and non-smokers, accounting for approximately 39% of all lung cancers.

The histopathologic spectrum of adenocarcinoma ranges from indolent to aggressive lesions. The initial Noguchi classification, published in 1995, first described the varying behavior of adenocarcinomas, which was also reflected in the World Health Organization (WHO) 2004 classification system. These systems used the term BAC for lepidic growth of tumor that failed to invade the stroma of the alveolar wall, with growth of cells along preexisting alveolar structures. The WHO system included AAH, a preinvasive lesion analogous to squamous dysplasia, and used the term adenocarcinoma, mixed subtype, for tumors that had BAC and invasive portions. In addition, the term BAC was applied to a variety of lesions, some with invasive features, thus hindering accurate characterization of these lesions.

More recently, the pathologic classification of lung adenocarcinoma has undergone revision.
Sponsored by the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society (IASLC/ATS/ERS), the newest classification incorporates knowledge related to advances in oncology, molecular biology, pathology, radiology, and surgery.3 According to the investigators, the new classification provides a uniform terminology for pathologic and small-biopsy diagnosis of lung adenocarcinoma, which includes molecular and immunohistochemical studies.3 The IASLC/ATS/ERS system eliminates the confusing term BAC as well as the designation of “adenocarcinoma, mixed subtype.” BAC is now replaced by the term “adenocarcinoma in situ” (AIS), representing lesions having only lepidic growth, lacking of invasion of any stroma, vessel, or pleura, and measuring 3 cm or smaller (Fig. 3).4 Nonmucinous histology is more frequent than mucinous in AIS.45 Similar to AIS, MIA has an excellent prognosis with a near 100% 5-year disease-free survival rate.3

Lesions previously classified as adenocarcinoma mixed subtype are now divided into multiple categories. The least invasive adenocarcinoma is the new diagnosis of minimally invasive adenocarcinoma (MIA), a predominantly lepidic lesion lacking necrosis and any invasion of lymphatics, blood vessels, or pleura and measuring 3 cm or smaller with an invasive component measuring no more than 5 mm in any one location (Fig. 5).3 MIA has an excellent prognosis with a near 100% 5-year disease-free survival rate.3

Invasive adenocarcinomas are subtyped histologically according to the main histopathological subtype and labeled as lepidic, acinar, papillary, micropapillary, or solid-predominant (Figs. 6 and 7). Lepidic-predominant adenocarcinoma (LPA) is composed of a nonmucinous tumor that demonstrates lepidic growth; however, the focus of invasion is larger than 5 mm in greatest dimension or contains tumor necrosis, invades lymphatics or blood vessels. LPA has been reported as having a 90% 5-year recurrence-free survival.45 Lepidic growth occurring due to mucinous tumor has been classified separately as invasive mucinous adenocarcinoma, previously termed mucinous BAC, with worse prognosis and different therapeutic considerations when compared with their nonmucinous counterparts.3 The prognosis is intermediate for the acinar and papillary predominant subtypes, and poor for the solid, micropapillary and invasive mucinous forms.46 Given the heterogeneous nature of these tumors, broad evaluation of the entire tumor is recommended to render a diagnosis.3

**Extrathoracic metastases**

The possibility of persistent subsolid nodules representing metastatic lesions rather than primary lung adenocarcinoma is extremely rare, even in cases with a known extrapulmonary malignancy (Fig. 8).47 Park and colleagues47 reported that among 59 GGNs in patients with a known extrapulmonary malignancy, none proved to be secondary to metastases. However, metastases have been reported to have ground-glass components. Okita and colleagues48 reported a case of metastatic

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**Table 1**

Computed tomography attenuation of adenocarcinoma entities

<table>
<thead>
<tr>
<th>Pure ground-glass nodule</th>
<th>AAH</th>
<th>Nonmucinous AIS &gt; part solid &gt; solid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part-solid</td>
<td>Nonmucinous AIS</td>
<td>Nonmucinous MIA &gt; ground-glass &gt; solid (variable, not fully described)</td>
</tr>
<tr>
<td></td>
<td>Lepidic predominant adenocarcinoma (variable not fully described)</td>
<td>Other adenocarcinoma histology</td>
</tr>
<tr>
<td>Solid</td>
<td>Mucinous AIS (nodule or consolidation)</td>
<td>Mucinous MIA &gt; part solid</td>
</tr>
<tr>
<td></td>
<td>Lepidic predominant adenocarcinoma</td>
<td>Other adenocarcinoma histology</td>
</tr>
<tr>
<td></td>
<td>&gt; part solid &gt; pure ground glass</td>
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**Abbreviations:** AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma.
melanoma presenting as a GGN that correlated with lepidic proliferation along the thickened alveolar walls without hemorrhage. Occasionally ground-glass and air-space patterns on CT have been identified infrequently with metastases to the lung from extrathoracic primaries and represent a preservation of the alveoli and spread of neoplastic cells along the alveolar septa.\textsuperscript{49,50} This has been reported by Gaeta and colleagues\textsuperscript{50} to occur in 6 of 56 patients with gastrointestinal carcinoma, 3 with pancreatic, 2 with colon, and 1 with jejunal carcinoma, respectively, and rarely in the renal cell cancers studied by Yanagawa and colleagues.\textsuperscript{49} Kang and colleagues\textsuperscript{51} have suggested that in patients with known melanoma, emphasis should be made on the growth rate of subsolid nodules, such that rapidly growing nodules are suspected to represent melanoma metastasis.

\textbf{Inflammatory etiologies}

Organizing pneumonia is another potential cause of persistent subsolid nodules. Organizing pneumonia is classified as either cryptogenic (idiopathic) or secondary, associated with a variety of conditions that include infection, malignancy, connective tissue disease, drug reaction, and radiation injury.\textsuperscript{52–54} One manifestation of organizing pneumonia on chest CT is the “reversed halo sign,” defined by the Fleischner Society glossary of terms as “a focal, rounded area of ground-glass opacity surrounded by a more or less complete ring of consolidation” (\textbf{Fig. 9}).\textsuperscript{4} Originally described with organizing pneumonia,\textsuperscript{19} more recent studies reported the presence of the reversed halo sign in a variety of infectious and noninfectious pulmonary disorders, indicating its nonspecific nature.\textsuperscript{55–58} However, organizing pneumonia is still considered the most common cause of the “reversed halo sign,” occurring in 12% to 19% of patients with organizing pneumonia.\textsuperscript{61}

Another potential cause of persistent subsolid nodules is focal lung fibrosis, presumably the sequela of prior inflammation or infection. Focal lung fibrosis has been described as a sharply demarcated GGO measuring smaller than 2 cm, with or without a solid component that may be related to alveolar collapse.\textsuperscript{62–64} Although some CT features, such as concave margins and polygonal shape, can help differentiate it from malignancy,\textsuperscript{62} there remains considerable overlap in

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig2}
\caption{AAH. (A) Axial 1-mm chest CT image in lung window show few pure GGOs in the right upper lobe (largest annotated by white arrow) representing foci of AAH. (B) Hematoxylin and eosin (H&E)-stained section shows a small (1.25 mm) dysplastic lesion (magnification ×40). (C) H&E-stained section shows mildly to moderately atypical type II pneumocytes lining alveolar walls; normal alveoli in upper right corner (magnification ×200).
}
\end{figure}
CT features of these 2 entities, rendering reliable differentiation between the 2 often challenging.

CT TECHNIQUE

CT technique for the diagnosis and accurate evaluation of subsolid nodules requires contiguous thin-section evaluation, optimally with 1-mm sections. With thin sections, a subsolid nature of a detected nodule can be confirmed and discriminated from small solid nodules that appear faint due to partial volume effect on thicker sections. Thin sections enable more accurate assessment of nodule size and of the presence and size of any solid component, factors correlating with patient prognosis and aiding in determining management. CTs performed for nodule evaluation use high-frequency reconstruction kernels that maximize spatial resolution, in contrast with low-frequency algorithms. Visualization of subsolid nodules in more than one plane, such as axial, coronal, or sagittal, enable better assessment of the 3-dimensional features of the entire nodule and of any solid components.

Given that multiple chest CT examinations may result from the follow up of nodules, attention to radiation dose reduction is essential. Dose reduction by reducing the tube current is recommended. CT technology available for reducing patient exposure includes tube current modulation, which modulates the tube current in the x, y, and z dimension and adjusts the overall tube current according to patient size to maintain a prescribed image quality. Automated tube-voltage selection is another method available for determining the optimal kilovolt potential setting according to patient size, with lower kilovolt potentials selected for smaller patients with potentially lower radiation exposures. Reducing the coverage in craniocaudal dimension is another method for reducing patient exposure.

The desire to minimize radiation exposure to patients needs to be balanced with the potential degradation in image quality resulting from increased image noise, which can potentially impair nodule detection. For example, Funama and colleagues reported decreased detection of simulated nodules of -800 HU when images using 21 mAs were compared with 180 mAs.

To reduce image noise, iterative reconstruction (IR) techniques have been introduced and are
now available from major CT vendors. IR compares projections from the raw data to modeled data while correcting for errors (such as noise and artifact) in several loops, thus creating an image closest to the true image. Singh and colleagues found that the filtered back projection (FBP) technique had unacceptable image noise at 40 and 75 milliampere second (mAs), whereas their IR technique had acceptable image noise at 40 to 150 mAs when subjectively evaluated. No lesions were missed using either technique. Higuchi and colleagues reported that the detection of simulated GGNs in a chest phantom was decreased on images performed at lower tube currents, such as 20 mAs (for both FBP and IR) and 50 mAs (for FBP) when compared with detection at 200 mAs. However, no difference in the detection of GGNs between 200 mAs (reconstructed with FBP) and 50 mAs (reconstructed with their IR algorithm) was identified. Knowledge of the effect of reduced tube current on GGN detection and the benefit gained with varying IR algorithms will increase with further investigation.

Fig. 4. Adenocarcinoma with a background of AAH. Axial chest CT images viewed in lung windows demonstrating a predominantly ground-glass PSN in the left upper lobe (A) with adjacent smaller GGOs (B, C). Following lobectomy, histopathology of the PSN (a) revealed invasive adenocarcinoma with lepidic and papillary patterns with a background of multifocal AAH corresponding to GGNs (white arrows in B, C).
CT CHARACTERIZATION

The ability of CT to distinguish benign from malignant causes is variable.\(^5,26,72,73\) Reliable CT features to confidently differentiate between malignant and benign causes of persistent subsolid nodules have not been identified. Margin and shape features have not been confirmed as differentiators of benign and malignant subsolid nodules, although some features have been reported to differ between the 2 groups. Kim and colleagues\(^26\) reported that polygonal shape and spiculated or lobulated margins were observed in both benign and malignant causes. For example, BAC or adenocarcinoma with BAC features had lobulated or spiculated margins in 45% and had polygonal shape in 25% of cases. Organizing pneumonia and fibrosis proved to be polygonal in shape in 20% and had lobulated or spiculated margins in 30%. Irregular and spiculated margins were caused by both granulation tissue in interstitial fibrosis and infiltrative tumor growth.\(^26\) In contrast, Lee and colleagues\(^72\) reported that polygonal shape and spiculated or lobulated margins were observed in both benign and malignant causes. For example, BAC or adenocarcinoma with BAC features had lobulated or spiculated margins in 45% and had polygonal shape in 25% of cases. Organizing pneumonia and fibrosis proved to be polygonal in shape in 20% and had lobulated or spiculated margins in 30%. Irregular and spiculated margins were caused by both granulation tissue in interstitial fibrosis and infiltrative tumor growth.\(^26\) In contrast, Lee and colleagues\(^72\) reported that lobulated nodule borders were predictive CT features of malignancy in 80 subsolid nodules. In a study by Takahashi and colleagues,\(^74\) a lobulated margin was one of the characteristics significantly associated with growth of pure GGNs. Li and colleagues\(^9\) reported that among both pure and mixed subsolid nodules, round shape was found more frequently in malignant than benign lesions; however, there was no significant association between smooth, irregular, or spiculated margins and malignancy.

Size, Internal Characteristics, and Associated Findings

Nodule size, internal features such as bubbly lucencies and air bronchograms, and associated findings including pleural tags and vascular convergence have been associated with malignancy (Figs. 10 and 11). Takahashi and colleagues\(^74\) in their 150 pGGNs identified a size larger than 10 mm and a bubblelike appearance to be significantly associated with nodule growth. According to Matsuguma and colleagues,\(^75\) a dimension larger than 10 mm predicted growth of nonsolid nodules, whereas Lee and colleagues\(^72\) identified

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**Fig. 5.** MIA. (A) Axial 5-mm chest CT image through the superior segment of the right lower lobe demonstrates a poorly marginated GGN. (B) H&E-stained sections show a circumscribed neoplasm composed predominantly of a lepidic pattern of growth (95%). There is also an area of fibrosis, highlighted by circle with an acinar pattern of invasion (5%) (magnification ×10). (C) Small angulated glands invade into a fibroelastic scar without myofibroblastic stroma (magnification ×200).
a size more than 8 mm of pGGNs to be an indicator of malignancy. Air bronchograms and bubblelike lucencies were not significantly predictive in some investigations, although recent investigations by Honda and colleagues and Takashima and colleagues reported notches, spiculations, and pleural tags to be more common in cases of invasive adenocarcinomas. A study by Aoki and colleagues reported the development or increase of pleural indentation, vascular convergence, or both more often in “mixed” GGOs than in pGGNs. Although not specific, the presence of air bronchograms and bubblelike lucencies in peripherally located subsolid nodules is suggestive of adenocarcinoma.

**Nodule Attenuation**

The CT appearance of subsolid adenocarcinomas varies according to lesion histology, with solid components positively correlating with invasion and ground-glass attenuation reflecting lepidic noninvasive tumor. Correspondence between CT morphology and histology has primarily been studied in relation to the Noguchi and WHO classifications and to a smaller degree using the system of the IASLC/ATS/ERS. Nonmucinous forms of preinvasive and minimally invasive lesions are associated with the subsolid nodule on CT. Preinvasive AAH most often manifests as a pGNN measuring less than or equal to 5 mm (see Fig. 3). The most common CT appearance of nonmucinous AIS is also that of a pGNN that is 3 cm and smaller. Occasionally, nonmucinous AIS can manifest as a part-solid or less typically a solid nodule. A study by Oda and colleagues demonstrated that spherical shape associated with AAH and air bronchograms with BAC (now termed AIS) were useful for differentiating between BAC and AAH. Nonmucinous MIA may appear on CT as a pGNN or a part-solid GGN predominantly 3 cm and smaller, where the solid component corresponds to the invasive (≤5 mm) component histologically, to be clarified by future studies (Fig. 12). Invasive adenocarcinomas usually present on CT as solid or...
part-solid GGNs and only rarely as a pGGN.\textsuperscript{2,85} Thus AAH, AIS, and MIA appear similar in attenuation as pGGNs whereas AIS, MIA, and invasive adenocarcinomas are considered when the nodule is subsolid. The greater degree of the solid component in a persistent subsolid nodule is an indicator of worse prognosis.\textsuperscript{28,86–92} In a study by Ikeda and colleagues\textsuperscript{86} of 115 resected nodules with a GGO ratio of less than 50%, lymph node involvement was present in 10.4% of cases, and the 5-year survival rate was 83.9%, compared with no lymph node metastasis and a 100% 5-year survival rate for the 44 nodules with a GGO ratio >50%. Another study by Ohde and colleagues\textsuperscript{92} showed that among 101 resected peripheral adenocarcinomas measuring smaller than 3 cm, the size of the solid component (solid to ground-glass ratio \( \leq 0.5 \)) was the best predictor of noninvasive adenocarcinomas, correlating with a 5-year survival rate of 95.7%. Of note, rarely mucinous forms of AIS and MIA occur. Mucinous AIS appears as a solid nodule. Mucinous MIA may present as a solid nodule.\textsuperscript{2} Invasive mucinous adenocarcinoma is the terminology used for prior mucinous bronchoalveolar carcinoma, has a varied appearance, with solid, mixed, or pure GGO in nodular to consolidative form.

Other causes of persistent nodules can present with soft tissue attenuation, such as organizing pneumonia and focal interstitial fibrosis. These entities can show considerable overlap in terms of their CT features with malignancy, necessitating surgical resection in some cases for definitive characterization. In a study by Kim and colleagues,\textsuperscript{26} no significant difference was noted between AAH or BAC and the fibrosis/organizing pneumonia groups in terms of nodule shape, margins, internal characteristics, and the presence of pleural tags. On the other hand, Yang and colleagues\textsuperscript{25} suggested that an oval or polygonal appearance of GGNs, especially when associated with satellite nodules, is suggestive of benign nature. Histopathologic correlates of the solid component in focal organizing pneumonia/interstitial fibrosis include fibrotic nodules, fibroblast plugs in alveolar or bronchiolar spaces, and chronic interstitial inflammatory cell infiltration and fibrosis.\textsuperscript{25} Pleural tags correspond to areas of peribronchiolar inflammation and atelectasis.\textsuperscript{25,93,94}

Fig. 7. Acinar predominant adenocarcinoma. (A, B). Contiguous 1-mm axial chest CTs show a complex part solid part ground-glass nodule with slight thickening of the adjacent pleura in the right lower lobe superior segment. (C) The tumor consists of acinar (50%), papillary (30%), and lepidic (20%) components (magnification \( \times 10 \)). The circle indicates the area seen in high power in (D). (D) Small angulated glands invade through a fibrotic stroma (magnification \( \times 200 \)).
Fig. 8. Increasing soft tissue in subsolid nodule. Axial 1-mm magnified images at baseline (A) and follow-up 8 months later. (B) A 14-mm PSN with similar size, yet the solid component increasing in size over an 8-month interval, indicating nodule growth. Patient had a history of breast cancer. Subsequent right upper lobe segmentectomy revealed primary lung invasive adenocarcinoma.

Fig. 9. Organizing pneumonia: 5-mm axial section in lung window showing a right lower lobe ground glass density with soft tissue density consistent with a “reversed halo sign.” Histopathologic examination was consistent with organizing pneumonia.

Fig. 10. Bubblelike lucencies. Axial 1-mm chest CT image through the left upper lobe showing a PSN containing bubblelike lucencies. Histopathologic examination following resection revealed invasive adenocarcinoma.
Nodule Measurement, Growth, and Follow-up

Nodule measurement is important for expressing nodule size, which is used for detecting and expressing nodule growth and for predicting patient prognosis in patients with proven malignancy. Measuring the size of subsolid nodules is challenging due to the low contrast of the ground-glass components with the surrounding lung parenchyma. In addition to the largest diameter, the bidimensional average and volume of the entire nodule are methods for conveying the degree of solid component.

Expressions of the ratio of the solid component to the overall nodule size, whether linear or by area, have been investigated as means to better characterize these lesions. For example, manually acquired linear and area measurements have been studied as methods to reflect the proportion of the solid region in subsolid nodules. Both semi and automated algorithms are under investigation. Soft tissue windows have been used as a method to threshold the solid components within a subsolid nodule, an approach termed the “vanishing ratio.” Investigated by Kakinuma and colleagues, this approach has also been termed the “tumor disappearance rate.” The vanishing ratio is computed using the formula

$$\frac{A_{I} - A_{m}}{A_{I}} \times 100\%,$$

where $A_{I}$ is the area of the entire nodule (on lung window) and $A_{m}$ is the area of the solid component when viewed using mediastinal window settings, both of which are typically determined by visual inspection and manual segmentation. This method was the most accurate predictor of a 5-year disease-free survival, when compared with other methods including conventional lesion length measurement.

More recently, advances with computer-assisted techniques have been explored. Sumikawa and colleagues, evaluating 49 patients with histologically proven adenocarcinomas measuring 2 cm or smaller, found that the solid component percentage determined using a semiautomated software...
Subsolid Nodules

Program was more reproducible than manually acquired measurements of the largest area or largest diameter. Interestingly, the correlation between measurements and histopathology was better for the manual method than with the automated software.\textsuperscript{95} Yanagawa and colleagues,\textsuperscript{91} using similar software for automated quantification of the solid component that automatically classified nodules into 1 of 6 subtypes, also reported good agreement with manual methods and were also useful in predicting lymphatic, vascular, and pleural invasion of 46 resected adenocarcinomas.

Nodule mass\textsuperscript{98,103} has been studied as a measure of size combined with density. Described by de Hoop and colleagues,\textsuperscript{103} GGN mass can be calculated by multiplying nodule volume and density. Volume can be determined by manually outlining the perimeter of the nodule followed by computerized calculation, whereas density is obtained by adding 1000 to the mean Hounsfield unit value of the nodule.\textsuperscript{104} In this preliminary study, De Hoop and colleagues\textsuperscript{103} reported that mass measurements allowed detection of GGN growth earlier than either diameter, area, or volume measurements and proved subject to less variability.

Although the optimal method for expressing the degree of soft tissue is not established yet, the correlation of the degree of soft tissue with patient prognosis is evident.\textsuperscript{91,95–97} A large study by Nakata and colleagues\textsuperscript{97} evaluating 146 resected T1N0M0 non-small cell lung cancers demonstrated good correlation of histologic classification, pathologic invasiveness, and postoperative outcomes with the percentage of GGO within tumors. Patients with greater than 50% ground-glass ratio were considered possible candidates for limited resection.\textsuperscript{97} Tateishi and colleagues\textsuperscript{96} suggested that the proportion of the non-solid component determined by volumetric analysis was a reliable predictor of tumors without vessel invasion in patients with lung adenocarcinoma. Furthermore, it has been shown for solid nodules that interobserver variation is decreased with automated measurement techniques.\textsuperscript{105,106} For subsolid nodules, less attention has been directed toward computer-assisted methods.\textsuperscript{107,108} Oda and colleagues\textsuperscript{107} studied the accuracy and reproducibility of computer-aided volumetry compared with manual volumetry in multidetector CT of GGNs, and reported a small relative measurement error (−4.1% to 7.1%) for nodules measuring 5 mm or larger. Interobserver and intraobserver agreement was relatively high for nodules measuring 8 mm or larger.

Follow-up CT is a well-recognized method for characterizing subsolid nodules. Risk factors for growth of subsolid nodules include large size (>10 mm) and history of lung cancer, as reported by several studies.\textsuperscript{109} Volume-doubling time (VDT) is a method for assessing nodule growth. The slower growth rate of lung cancers manifesting as subsolid nodules as compared with those presenting as solid nodules has been well established.\textsuperscript{10,111} A study by Hasegawa and colleagues\textsuperscript{110} evaluating 61 lung cancers detected by CT screening reported a mean volume doubling time of 813 days for pGGNs, compared with 457 days for part-solid GGNs and 149 days for solid nodules. Another retrospective study by Oda and colleagues\textsuperscript{111} using computer-aided 3-dimensional volumetry for assessment of 46 GGNs histologically proven to be AAH, BAC, or adenocarcinoma, reported a significantly shorter VDT for mixed compared with pGGNs (276.9 ± 155.9 days vs 628.5 ± 404.2 days, respectively). VDT was also significantly shortest for adenocarcinomas, followed by BAC and then AAH.\textsuperscript{111}

Subsolid nodule growth on CT is indicated by an increase in the overall size of the nodule but also any development of or progression in any solid components (see Fig. 8).\textsuperscript{112–114} In a study by Takashima and colleagues,\textsuperscript{30} 75% of the lesions presenting initially as pGGNs showed subsequent increase in size; 17% developed a solid component; increasing soft tissue was identified in 23%. In some instances, subtle changes in CT density or the solid component are better appreciated on serial examinations, necessitating the comparison with remote rather than just the immediate prior examinations. Malignant nodules have been reported in addition, due to the development of fibrosis, to initially decrease and then increase in size.\textsuperscript{115} Takashima and colleagues\textsuperscript{30} reported tissue contraction in 6% of their lung cancers. Thus, a nodule that initially decreases on a subsequent CT may therefore need further follow-up imaging to establish long-term stability or resolution (Fig. 13).

ROLE OF PET-CT AND TRANSTHORACIC/TRANSBRONCHIAL BIOPSY

FDG PET-CT is of limited value in the evaluation of subsolid nodules, particularly pGGNs measuring smaller than 10 mm.\textsuperscript{116–123} GGNs are unlikely to show FDG activity, and the probability of occult nodal and distant metastasis associated with this type of lesion is low.\textsuperscript{124–127} For instance, Yap and colleagues\textsuperscript{128} evaluated surgically proven adenocarcinomas and reported that 67% of pure BAC lesions without invasion had no FDG uptake. However, a potential role for FDG PET-CT, in conjunction with thin-section chest CT, exists for
evaluating part-solid GGNs, in particular those exhibiting a solid component measuring greater than 10 mm. Several studies reported increasing FDG activity with increasing aggressiveness and histology of lung adenocarcinomas. Tsunezuka and colleagues in a retrospective study of 37 patients with peripheral lung cancers measuring 2 cm or smaller concluded that PET/CT could not differentiate benign from malignant entities, as 16 (61.5%) of 26 of Noguchi types A, B, and C adenocarcinomas, which correspond to AAH, AIS, and MIA in the IASLC classification, were falsely negative on PET-CT, whereas 9 (31.8%) of 11 of types D, E, and F (invasive adenocarcinomas) were true positives. Similarly, Goudarzi and colleagues demonstrated lower FDG uptake for BAC compared with adenocarcinoma with BAC components. FDG PET-CT has a major role in nodal staging for decisions pertaining to surgical resection; limited surgical resection is under investigation for patients with subsolid nodules in whom nodal metastases are not identified.

In patients who are surgical candidates, transthoracic or transbronchial biopsy is not routinely recommended for evaluation of subsolid nodules, given the lower diagnostic yield and difficulty in accurately differentiating AAH, MIA, and different subtypes of invasive adenocarcinoma on small biopsy samples. For CT-guided transthoracic needle biopsy of small lesions (<2 cm, including GGOs and PSNs), the overall diagnostic yield has been reported to be as low as 65%, with yields of 51% for all GGO-dominant lesions and only 35% for GGO-dominant lesions measuring smaller than 10 mm. Other investigations have reported higher diagnostic rates, with overall accuracy rates of 91% for nodules measuring both 2 cm or smaller and 2 cm or larger, with various GGO components. Accurate pathology diagnosis now requires review of the entire lesion given the mixed histology, which cannot be performed on small biopsy samples. For this reason surgical sampling is recommended. Transthoracic or transbronchial biopsy, however, remains an option when patients are nonsurgical candidates, surgical candidates for whom histologic proof of malignancy is deemed necessary, or in patients with multifocal disease.

Surgical resection is the favored method for histologic diagnosis of subsolid nodules.

**MANAGEMENT OF SUBSOLID NODULES**

Guidelines and recommendations for the management of the subsolid nodule have been issued. In January 2013, the Fleischner Society published recommendations for management of subsolid nodules to complement the original guidelines for management of solid nodules in 2005. In contrast to the guidelines for solid nodules, those for subsolid nodules do not alter recommendations according to risk factors, such as smoking. For subsolid nodules, the guidelines address whether the nodules are multiple or solitary with differing recommendations for multiple GGNs depending on whether there is or is not a
dominant lesion. Follow-up imaging is advised for a minimum of 3 years, given that slow growth can occur, in distinction to 2 years recommended for solid nodules. In addition, size is less of a factor for determining management. The recommendations for subsolid nodules greater than 5 mm do not consider overall size as a factor.

Guidelines include assessment for the presence of solid attenuation that has been shown to correlate with invasive features in adenocarcinomas; more aggressive management may be indicated in this scenario.\(^{28,86–92}\) For evaluation of subsolid nodules, guidelines indicate the use of thin-section (1 mm) CT to accurately characterize nodule attenuation and other features in addition to low-dose technique to minimize radiation exposure. For each of the recommendations, 3 for solitary subsolid nodules and 3 for multiple nodules, specific aspects are assigned a grade and the quality of the evidence.\(^{1,136}\) For solitary pGGNs measuring 5 mm or smaller, follow-up CT surveillance is not required. The probability of progression to adenocarcinoma is low, and detection of growth of these nodules with very slow doubling time is subject to substantial interobserver and intraobserver variability using currently available conventional measurement techniques. The investigators indicate that these nodules are unlikely to represent metastatic disease in patients with a known extrathoracic malignancy.

For solitary pGGNs measuring larger than 5 mm, the recommendation is to obtain an initial follow-up at 3 months, followed by annual surveillance for a minimum of 3 years, except if the size of the solid component exceeds 5 mm, in which case biopsy or surgical resection would be advised. The purpose of the initial CT is to confirm the persistence of the nodule and evaluate for any aggressive behavior and rapid growth that can occur, such as with a less common mucinous neoplasm. The pGGNs larger than 5 mm most likely represent AAH, AIS, or MIA and, less likely, invasive carcinomas although, as previously noted, up to 20% of persistent pGGNs have been reported to be inflammatory in etiology.\(^{26}\) Part-solid nodules have a higher likelihood to be malignant, and management is performed in light of this with a follow-up CT at 3 months to confirm persistence and evaluate for growth. Subsequent more conservative management can be considered for PSNs with solid portion 5 mm or smaller given their correlation with MIA or AIS. It cannot be overemphasized that a decrease in size of lesions on follow-up examinations does not necessarily correlate with a benign etiology: this may occur in malignancy as a result of focal fibrosis within malignant lesions causing a spurious appearance of resolution.

Multiplicity is addressed for subsolid nodules. For multiple pure GGNs, the authors recommend follow-up at 2 and 4 years for lesions measuring 5 mm or smaller. Patients with multiple pGGNs, with one larger than 5 mm without a dominant lesion, are suggested to have follow-up at 3 months initially followed by annual surveillance for a minimum of 3 years. For multiple nodules with a dominant nodule that has part-solid or solid components, they recommend reassessment at 3 months and if persistent biopsy or surgical resection, especially if the solid component exceeds 5 mm in size. FDG PET can be misleading when evaluating pure ground-glass nodules larger than 5 mm, whereas a possible role exists for part-solid nodules.

More recently the ACCP has also published recommendations for the management of nodules, both solid and subsolid. Although guidelines are similar to those of the Fleischner Society, there are noticeable differences (Box 2 and Table 2). Importantly, the ACCP guidelines primarily focus on solitary rather than multiple lesions. They also emphasize the nodule size specifically 8 mm for the solid component of part-solid lesions and 10 mm for pGGNs. More importantly, unlike the Fleischner guidelines, the ACCP guidelines consider the pretest probability for malignancy and the surgical candidacy of the patient. The pGGNs 5 mm or smaller are managed in the same manner as in the Fleischner guidelines.\(^{137}\) The pGGNs larger than 5 mm are recommended to have annual follow-up for at least 3 years. A 3-month follow-up chest CT is suggested for those larger than 10 mm and followed by nonsurgical biopsy and/or surgical resection if persistent. For PSNs that are 8 mm and smaller, CT surveillance at approximately 3, 12, and 24 months followed by annual CT for an additional 1 to 3 years is recommended. For nodules larger than 8 mm, the recommendation is for repeat chest CT at 3 months, followed by further evaluation with PET-CT, biopsy, and/or surgical resection. PSNs larger than 15 mm are recommended to undergo

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**Box 2**

**Fleischner Society and ACCP Management guidelines similarities**

**Similarities**
- No follow-up for pure ground-glass nodules (pGGNs) <5 mm
- Yearly follow-up for pure GGNs >5 mm × 3 years
- Emphasis on low-dose studies
- No emphasis on nodule morphology
further assessment with PET, nonsurgical biopsy, and/or operative resection. For patients with a dominant nodule and one or more additional nodules, the ACCP suggests that each nodule be treated individually with curative intent unless metastasis is proven histopathologically. Specific guidelines are not indicated in terms of chest CT follow-up for multiple nodules in the ACCP guidelines.

**Surgical Resection**

Surgical resection is the mainstay of treatment for subsolid nodules. Although with 100% or near 100% 5-year disease-free survival rate of AAH, AIS, and MIA have been reported, greater understanding is needed to further refine indications for surgery. More immediately, although still controversial, a number of studies have supported limited sublobar resection, including wedge resection and segmentectomy for subsolid nodules measuring 2 cm or smaller in place of lobectomy, with no significant difference in survival and locoregional recurrence rates. For example, in a 13-year analysis study by El-Sherif and colleagues, there was no significant difference between survival and recurrence rates in the sublobar and lobar resection groups. Whether limited surgical resection becomes a standard of care for small (≤2 cm) peripheral subsolid nodules awaits the results of 2 large randomized trials of the Japan Clinical Oncology Group (JCOG) 0802 in Japan and Cancer and Leukemia Group B (CALGB) 140503 in North America.

**SUMMARY**

Subsolid nodules, including both pGGNs and part-solid GGNs, relate to inflammatory and neoplastic etiologies. When persistent, they have a high likelihood of representing invasive lung adenocarcinomas and preinvasive lesions. Solid components within subsolid nodules on CT are associated with development of aggressive features. Nodule growth is reflected in some instances by increase in the solid component or any subtle change in internal characteristics. Recently published guidelines from the Fleischner Society should serve as useful guides to manage subsolid nodules.


47. Park CM, Goo JM, Kim TJ, et al. Pulmonary nodular ground-glass opacities in patients with extrapulmonary cancers: what is their clinical significance and how can we determine whether they are malignant or benign lesions? Chest 2008;133:1402–9.


