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REVIEW

Incidental, subsolid pulmonary nodules at CT: etiology and management

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Abstract

Pulmonary nodules, both solid and subsolid, are common incidental findings on computed tomography (CT) studies. Subsolid nodules (SSNs) may be further classified as either pure ground-glass nodules or part-solid nodules. The differential diagnosis for an SSN is broad, including infection, organizing pneumonia, inflammation, hemorrhage, focal fibrosis, and neoplasm. Adenocarcinomas of the lung are currently the most common type of lung cancer, representing 30–35% of all primary lung tumors, and the subtype of bronchioloalveolar cell carcinoma (BAC) commonly presents as an SSN. In 2011, a new classification system for lung adenocarcinomas was proposed by the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society. An important feature of the new system is the relinquishment of the term BAC in favor of more specific histologic subtypes. It has been reported that these subtypes are associated with characteristic CT findings. This article reviews the new classification system of lung adenocarcinomas, discusses and illustrates the associated CT findings, and outlines the current recommendations for further diagnosis, treatment, and follow-up of SSNs based on computed tomography findings.

Keywords: *Subsolid nodule; ground-glass nodule; part-solid nodule; lung adenocarcinoma; chest CT.*

Introduction

Pulmonary nodules are common incidental findings on computed tomography (CT) studies. These lesions may be classified as either solid or subsolid nodules (SSN), based on CT characteristics. SSNs may be further classified as either pure ground-glass nodules (GGNs) or part-solid nodules (PSNs). Pure GGNs demonstrate a focal hazy opacity through which the normal parenchymal architecture is visualized (Fig. 1). In contrast, PSNs have both ground-glass and solid components (Fig. 2). SSNs may also occasionally demonstrate bubble-like lucencies (Fig. 3).

The differential diagnosis for an SSN is broad, including infection, organizing pneumonia, inflammation, hemorrhage, focal fibrosis, and neoplasm. Adenocarcinomas of the lung are currently the most common type of lung cancer, representing 30–35% of all primary lung tumors and the subtype of bronchioloalveolar cell carcinoma (BAC) commonly presents as an SSN[1]. BAC typically follows an indolent clinical course, is less commonly associated with smoking compared with other non-small cell lung cancers (NSCLCs), and tends to affect a younger population. In addition, the presence of other pulmonary diseases, such as fibrotic disorders, increases the risk of developing BAC.

There is evidence that preinvasive lung lesions, classified as foci of atypical adenomatous hyperplasia (AAH), may progress to BAC and finally to invasive adenocarcinoma (Fig. 4)[1]. In 2011, a new classification system for lung adenocarcinomas was proposed by the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) (Fig. 5)[2]. An important feature of the new system is the relinquishment of the term BAC in favor of more specific histologic subtypes. It has been reported that these subtypes are associated with characteristic CT findings, as detailed below (Fig. 5). However, the use of this new classification system is controversial among pathologists due to significant interobserver

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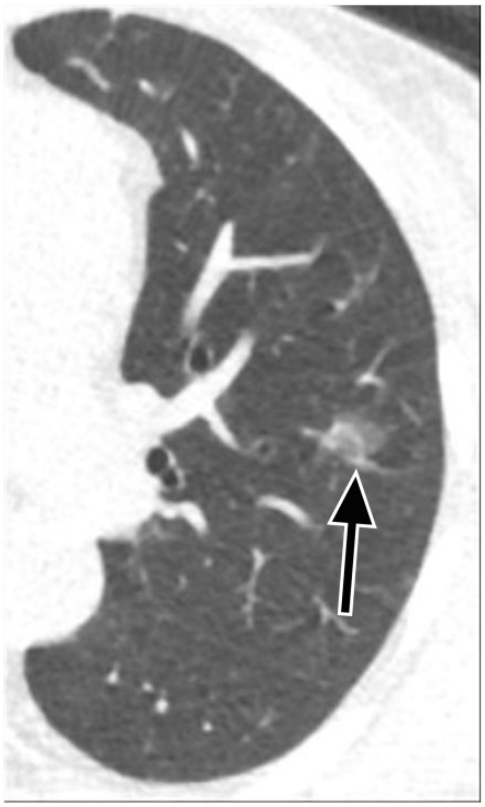

Figure 1 **A pure GGN (arrow) demonstrates a focal hazy opacity through which the normal pulmonary parenchymal architecture is visualized.**

variability in classifying specific lesions, and therefore many pathologists have not adopted the system to date.

New classification of lung adenocarcinomas and CT findings

AAH

The first category of the IASLC/ATS/ERS classification system is AAH. It is the earliest preinvasive lesion detectable by CT. Histologically, it is described as focal proliferation of atypical cuboidal or columnar epithelial cells along alveoli and respiratory bronchioles. On CT images, AAH typically manifests as small (usually <5 mm), frequently multiple, subtle, rounded GGNs with adjacent normal lung parenchyma and smooth margins (Figs. 5 and 6)[3].

Adenocarcinoma in situ

Adenocarcinoma in situ (AIS) joins AAH under the category of preinvasive lesions for lung adenocarcinoma, demonstrating a small nodule (<3 cm) with purely lepidic (bronchioloalveolar) growth and without stromal, vascular, or pleural invasion. On CT, AIS appears as a pure small GGN, which makes it difficult to distinguish from AAH, except that AIS is typically larger than

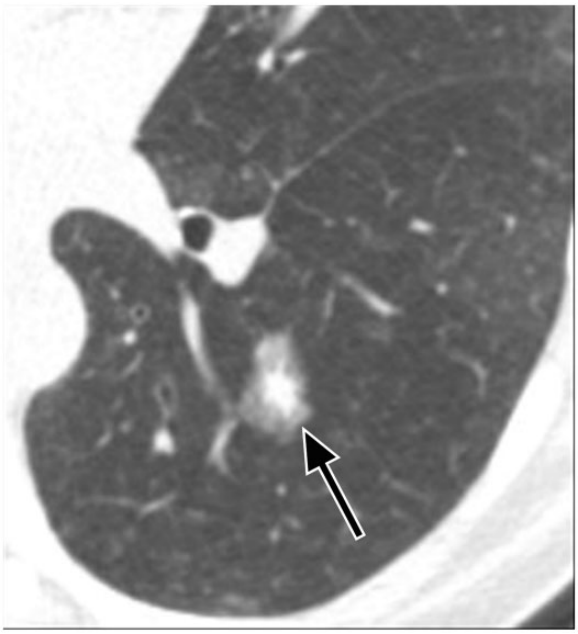

Figure 2 **A part-solid nodule (arrow) shows both ground-glass and solid components.**

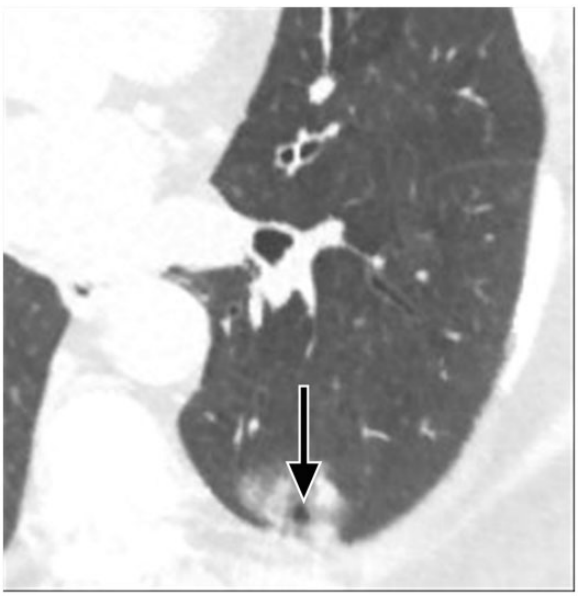

Figure 3 **A low-dose chest CT scan shows a part-solid nodule with bubble-like lucencies (arrow).**

5 mm (Figs. 5 and 7)[3]. AIS lesions demonstrate a very slow growth rate. Reportedly, complete resection of an AIS lesion is associated with 100% survival[2].

Minimally invasive adenocarcinoma

Minimally invasive adenocarcinoma (MIA) is the other new entity in the recently proposed classification system. MIA is a small (<3 cm) solitary adenocarcinoma with a

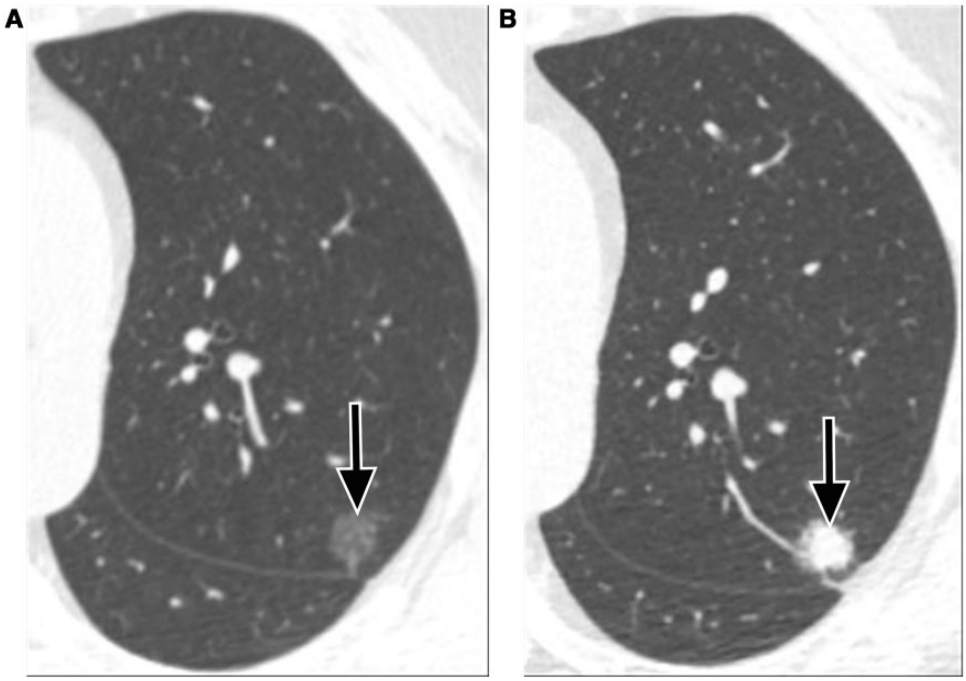

Figure 4 **1.25-mm thick sections through the left upper lobe obtained over a 4-year interval (a, baseline; b, 4 years) show change from a pure GGN to a part-solid nodule, which subsequently proved to be poorly differentiated invasive adenocarcinoma.**

	IASLC/ATS/ERS 2011	CT findings
	AAH (Atypical adenomatous hyperplasia)	Ground glass
BAC (Bronchiolo-alveolar carcinoma)	**AIS** (Adenocarcinoma in situ) ≤ 3 cm diameter	Ground glass, possible small solid component or bubble–like lucencies
	MIA (Minimally invasive adenocarcinoma) ≤ 3 cm diameter ≤ 5 mm invasion	Ground glass or part solid nodule; < 5 mm central solid component
	Invasive adenocarcinoma (non-mucinous or mucinous)	Part solid or solid; occasionally ground glass or bubble-like lucencies

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Figure 5 **Pathology-CT correlation.**

predominantly lepidic pattern, but it is distinguished by a small invasive component measuring no more than 5 mm in greatest dimension (Fig. 8)[2]. Early studies highlight low rates of interobserver agreement for assigning tumors to this category due, in part, to lack of consensus regarding those features that define early invasion in otherwise well-differentiated adenocarcinomas with lepidic-predominant growth patterns[4]. MIA may present as a GGN or a PSN with a small (typically <5 mm), central solid component; this solid component may represent fibrosis, atelectasis, or invasive cancer (Fig. 5). MIA is nearly always non-mucinous[2]. However, for the rare mucin-producing MIA, the mucin may contribute to a solid or part-solid appearance of the tumor at CT[2]. Therefore, the size of the solid component seen on CT may be larger than the truly invasive portion of the adenocarcinoma. It has been reported that complete resection of an MIA leads to nearly 100% survival[2].

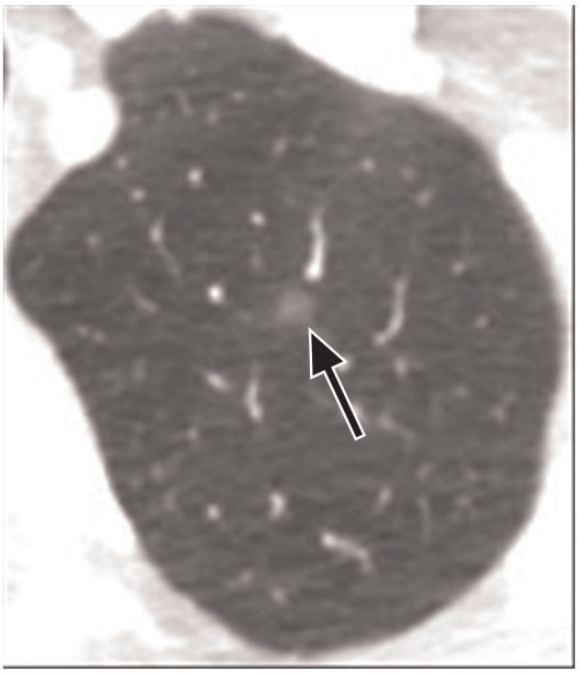

Figure 6 **1.25-mm thick section through the left upper lobe shows a small (<5 mm diameter) rounded GGN (arrow) with smooth margins and adjacent normal parenchyma, consistent with a focus of AAH.**

Invasive adenocarcinoma

Invasive adenocarcinomas consist of a complex mixture of histologic subtypes, including acinar, papillary, micropapillary, solid, and lepidic[2]. Invasive adenocarcinoma is usually visualized as a solid nodule, but may also be a PSN or occasionally a GGN (Fig. 5). The size of the tumor and the presence of spiculations both correlate with invasion[3].

Another major modification in the new classification system is the change in terminology from mucinous BAC into the same subsets proposed for non-mucinous adenocarcinomas measuring no more than 3 cm in greatest dimension (i.e., mucinous AIS, mucinous MIA, and invasive mucinous adenocarcinoma). Histologically, these tumors are distinguished by a population of mucinous tumor cells, which consist of tall columnar cells with abundant apical mucin and small basally oriented nuclei[2]. These tumors are often multifocal and multilobar[2]. A wide variety of findings can be seen at CT, such as consolidation, air bronchograms, and multifocal or multilobar solid and subsolid nodules or masses[2]. Lower lobe predominance is common for both the localized and multifocal forms of this disease (Fig. 9)[2].

Positron emission tomography scans

[^{18}F]Fluorodeoxyglucose (FDG)-positron emission tomography (PET) may help distinguish between malignant and benign lesions because cancers tend to show high metabolic activity and generally accumulate FDG more avidly compared with benign nodules. Approximately 95% of patients with a malignant nodule have an abnormal FDG-PET scan and 78% of patients with a benign lung nodule have a normal scan[5]. Thus, a negative PET scan correctly excludes lung cancer in most cases, but a positive PET scan may incorrectly identify infectious, inflammatory, or granulomatous nodules as malignant with considerable frequency[6]. False-negative scans may, however, occur in tumors with low metabolic activity, such as AIS or MIA, small lesions (a critical mass of metabolically active malignant cells is required for detection by PET) and in other situations, such as uncontrolled hyperglycemia (Figs. 10 and 11)[6].

Although PET/CT is a valuable tool for staging NSCLC by improving detection of local and distant metastases, its use in staging cancers manifesting as pure GGNs is limited because of the very low probability of nodal and distant metastases associated with these lesions[7]. PSNs with >50% ground-glass component are also unlikely to show nodal or distant metastases[7].

Management

Traditionally, a nodule that has remained stable for 2 years or longer on a chest radiograph is considered benign. However, this 2-year cutoff is arbitrary. One study reported that lack of appreciable growth on a chest radiograph over a 2-year period had a positive predictive value of only 65% for a benign lesion[8]. It is well known that certain cell types (e.g., low-grade adenocarcinomas and carcinoid tumors) may maintain an apparently stable size for 2 years or longer[8]. In general, solid cancers tend to grow quickly, whereas GGNs grow very slowly, and PSNs grow at a rate in between the two[9]. Thus, a low-grade adenocarcinoma with morphologic features of an SSN at CT and apparent stability over a 2-year period could easily be mistaken for a benign lesion.

The 2005 Fleischner Society guidelines for the management of small, incidental lung nodules discovered at CT were primarily focused on solid nodules[9]. However, given the higher chance of malignancy and slower growth rate of SSNs compared with solid nodules, these guidelines are probably not well suited to the management of SSNs. Thus, in 2013, new Fleischner Society guidelines were proposed specifically for the management of SSNs[10]. Unlike the 2005 guidelines, the new guidelines for SSNs do not differentiate between smokers and nonsmokers and do not specify a minimum patient age; this is because of the increasing incidence of adenocarcinomas in non-smoking and younger individuals. According to these new guidelines, follow-up CT examinations should use consistent methods with thin (e.g., 1-mm thick), contiguous (or overlapping) sections obtained with a low-dose technique. Recommendations from the

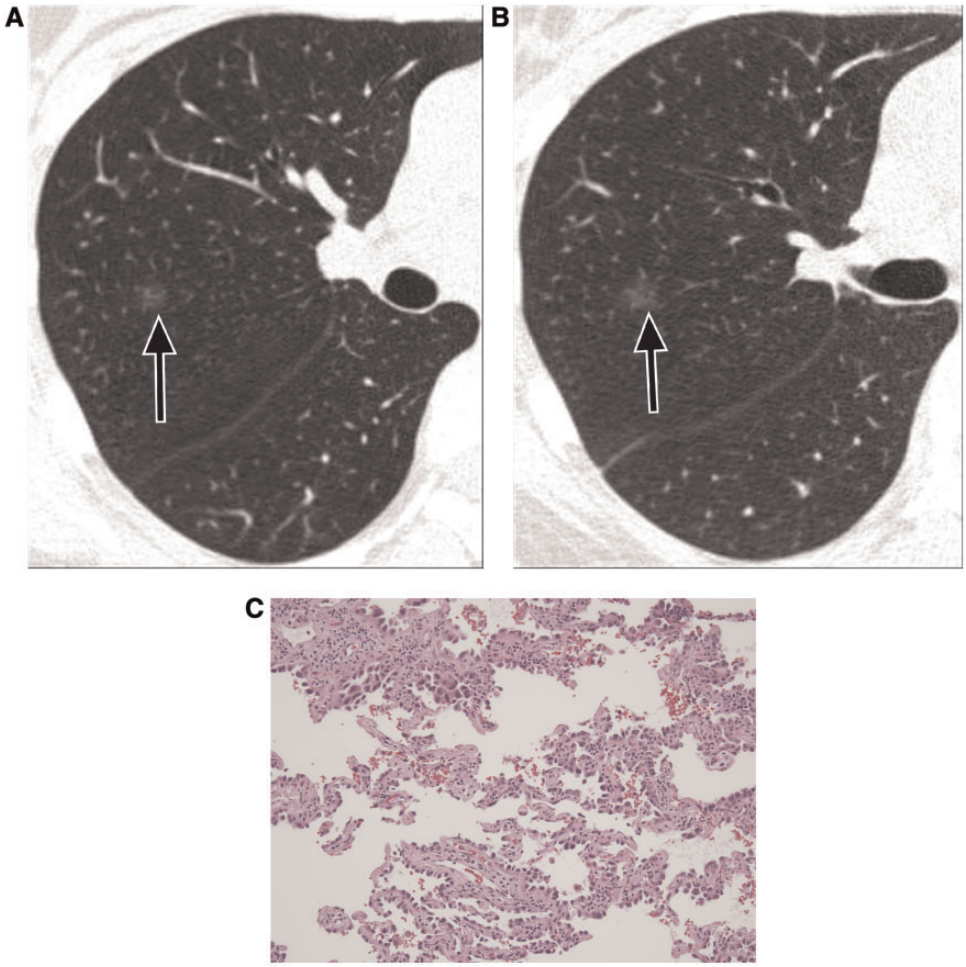

Figure 7 **1.25-mm thick sections through the right upper lobe obtained over a 3-year interval (a, baseline; b, 3 years) show growth of a pure GGN (arrow). The lesion was resected, and a high magnification photomicrograph (C) shows a well-differentiated non-mucinous AIS (hematoxylin and eosin stain; original magnification 200 ×). Enlarged neoplastic cells are distributed along intact alveolar septa with no associated invasion.**

guidelines are summarized below. It is important to remember that these recommendations must be used in the context of a patient's individual clinical situation.

Recommendation 1

A single pure GGN less than 5 mm requires no further follow-up imaging

These lesions are likely small benign areas of AAH and thus do not require further CT surveillance. There is a known association between AAH and adenocarcinoma, but it is unclear how often AAH actually progresses to invasive adenocarcinoma. Furthermore, studies have shown that these types of lesions often remain stable or show very indolent growth over long time periods of many years[11].

Recommendation 2

A single pure GGN larger than 5 mm requires an initial follow-up CT at 3 months followed by yearly CT scans for a minimum of 3 years as long as the lesion is persistent and stable in size

A pure GGN that is larger than 5 mm is likely to be a preinvasive AAH or AIS and is amenable to a conservative approach with CT surveillance[12]. The initial 3-month follow-up CT is done to identify the pure GGNs that spontaneously disappear, as well as the rapidly growing nodules. It should be noted that choosing to delay aggressive treatment in order to obtain an additional CT scan should not have any harmful effects on the patient[13].

When following these lesions with annual CT scans, the same measuring technique should be used each time to decrease inter- and intra-observer variability. Currently, there are no validated methods to measure changes in nodule size or attenuation. For those pure GGNs that appear to enlarge and/or increase in attenuation, surgical resection should be considered. Patients who are not surgical candidates should be considered for lung biopsy in order to establish a diagnosis of

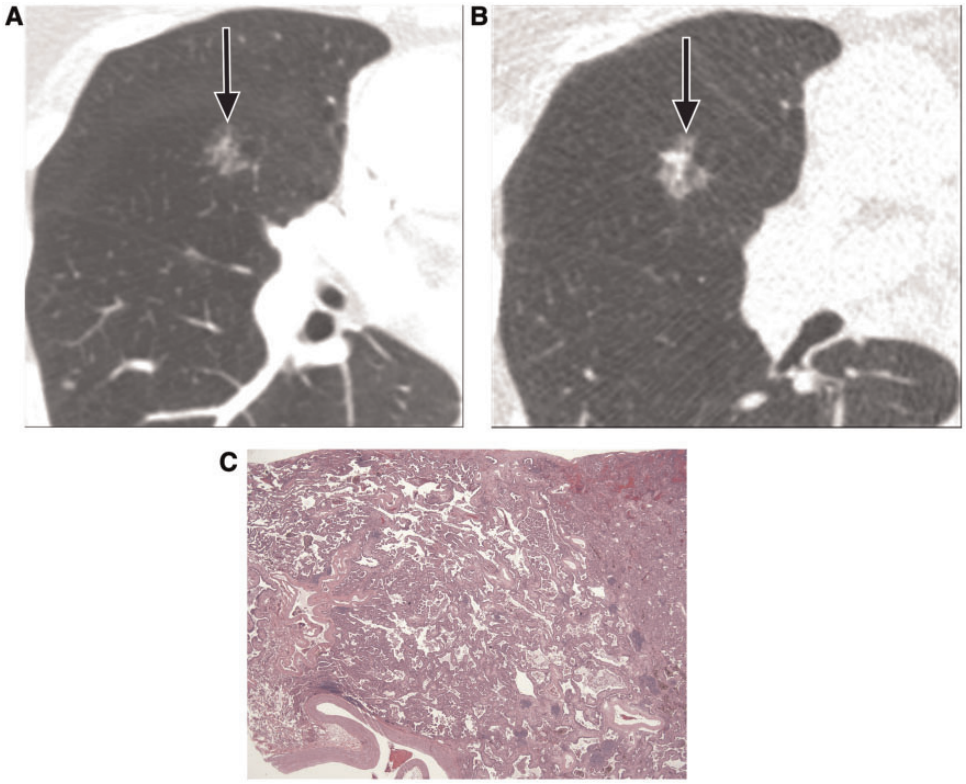

Figure 8 **1.25-mm thick sections through the right middle lobe obtained over a 3-year interval (a, baseline; b, 3 years) show growth of a part-solid nodule (arrow) with increase in size of the central solid component. The lesion was resected, and a low magnification photomicrograph (c) shows a well-differentiated microinvasive non-mucinous adenocarcinoma (hematoxylin and eosin stain; original magnification 20 ×). The bulk of the tumor shows a lepidic (bronchioloalveolar) growth pattern in which neoplastic cells are distributed along intact interstitial structures. In the upper right portion of the photomicrograph, neoplastic cells are arranged in a more complex acinar growth pattern with stromal invasion measuring less than 6 mm in greatest dimension. The area of invasion has a more solid appearance at low magnification.**

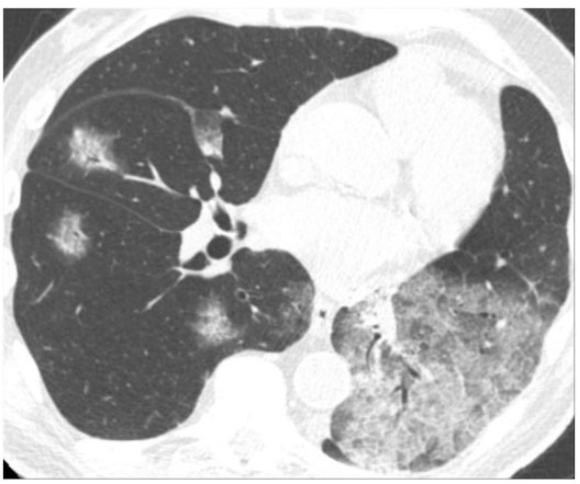

Figure 9 **CT through the lower lungs demonstrates bilateral ground-glass opacities. Histologic examination of a biopsy specimen revealed multifocal invasive mucinous adenocarcinoma.**

cancer and plan for appropriate therapy. However, neither transbronchial nor percutaneous CT-guided biopsy should be performed in patients who are deemed surgical candidates, because of the low diagnostic yield and significant risk of a false-negative biopsy result[14]. If the pure GGN is unchanged but remains larger than 10 mm, these same recommendations apply. There are no current recommendations for treating these lesions with a course of antibiotics to see if these lesions resolve[15].

Recommendation 3

A single PSN is considered malignant until proven otherwise if it remains stable or grows on a 3-month follow-up scan

An initial 3-month follow-up CT is recommended with PSNs to ensure persistence[16]. Malignant lesions may occasionally show a temporary decrease in size, due to contraction of a fibrotic or atelectatic component, and

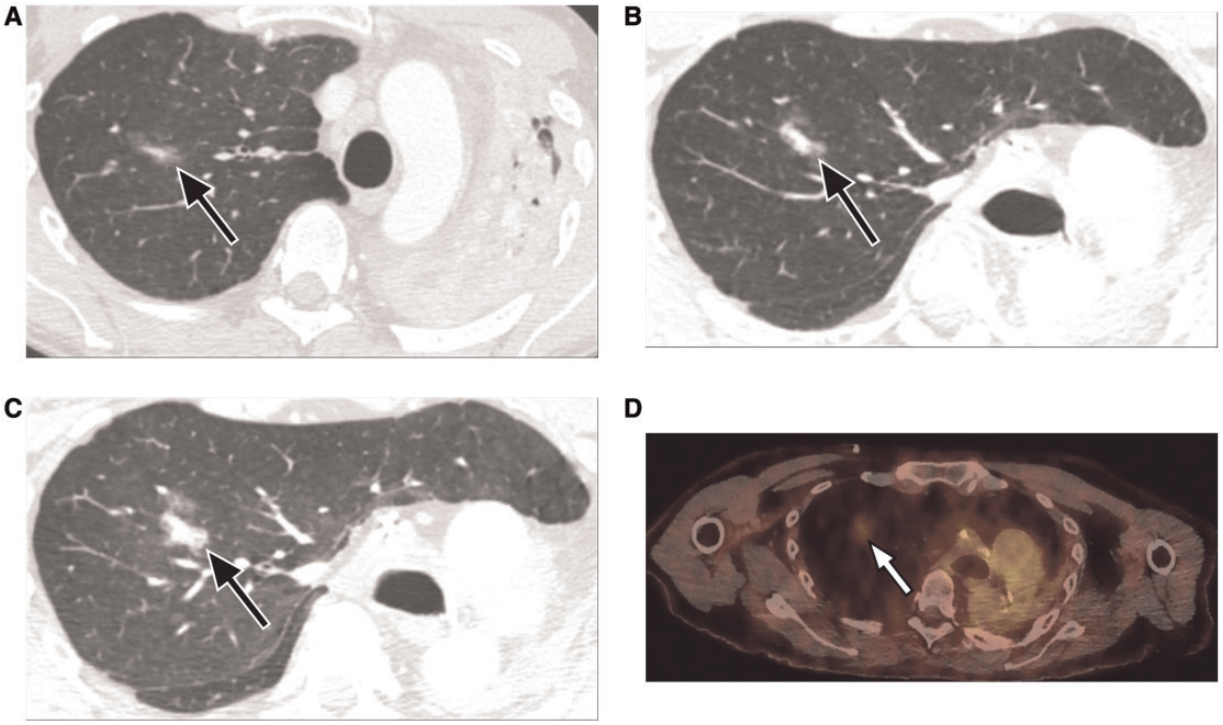

Figure 10 **1.25-mm thick sections through the right upper lobe obtained over a 3-year interval in a man with a previous left pneumonectomy for squamous cell lung cancer (a, baseline; b, 2 years; c, 3 years) show growth of a part-solid nodule (arrow). FDG-PET/CT (d) obtained at the 2-year time point reveals minimal activity within the nodule (arrow). Because the patient was already under treatment for biopsy proven squamous cell cancer recurrence elsewhere in the body, and due to the danger of a lung biopsy in a patient with a single lung, no tissue proof was obtained for this presumed indolent, primary lung adenocarcinoma.**

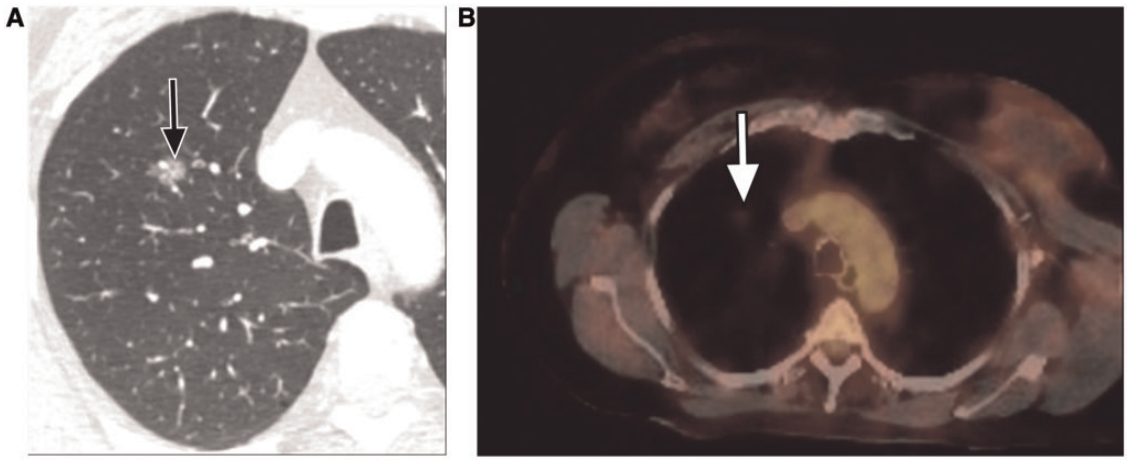

Figure 11 **1.25-mm thick section through the right upper lobe shows a GGN (arrow). FDG-PET/CT demonstrates no significant activity within the nodule (arrow). The nodule was subsequently resected and histopathologic examination revealed mucinous AIS.**

therefore a slight decrease in size should not constitute evidence of benignancy[17].

A solid component associated with a GGN is worrisome for invasive adenocarcinoma[18]. An important exception to this rule is when the solid component is less than 5 mm, because these lesions are more likely to be AIS or MIA; these lesions may be treated conservatively, as stated in recommendation 2. Studies have

shown that the greater the percentage of solid component, the more likely the lesion is to be invasive adenocarcinoma, with a poor prognosis[19]. In addition, increased overall nodule attenuation, even without a frank soft tissue component, also correlates with malignancy[20,21].

Although there is currently no standard approach to quantitatively assess these lesions, it has been suggested that the sizes of both the solid and ground-glass components should be acquired using the average of bidimensional measurements; measurements of the solid components should be obtained using soft tissue windows and of the ground-glass components using lung windows. Furthermore, CT scanning techniques should be consistent across examinations. When assessing for subtle change over time, the examination should be compared with the oldest available study.

Similar to the recommendation for pure GGNs larger than 5 mm, biopsy should only be performed if the patient is not a surgical candidate. If surgery is performed, a limited resection using a wedge or segmental resection rather than lobectomy may be considered, given the low likelihood of local tumor spread[18,22,23].

For PSNs measuring 8–10 mm in size, a PET scan may be obtained before surgery to optimize pre-operative staging[24].

Recommendation 4

Multiple pure GGNs all of which are smaller than 5 mm should be managed with follow-up CT scans at 2 and 4 years

As previously mentioned, GGNs that are smaller than 5 mm likely represent AAH, and conservative management is recommended[11]. In situations with multiple GGNs, alternative diagnoses should also be considered, such as respiratory bronchiolitis in smokers.

Recommendation 5

Multiple pure GGNs with at least 1 lesion larger than 5 mm and no identifiable dominant lesion should have a 3-month follow-up CT scan followed by subsequent yearly CT scans for at least 3 years. This is the same recommendation as for a solitary GGN larger than 5 mm.

Recommendation 6

The algorithm for multiple PSNs in which a dominant lesion can be identified is an initial 3-month CT scan, with further management dictated by the dominant lesion. An aggressive approach is recommended for lesions with a solid component larger than 5 mm.

Although there is no standard method to define a dominant lesion, PSNs with certain characteristics should be considered highly suspicious for cancer. These characteristics include a solid component larger than 5 mm, a pure GGN larger than 10 mm, spiculated contours, bubbly appearance, solid components smaller than 5 mm that show interval increase in size or attenuation. In these instances, surgery should be considered if the patient is a surgical candidate[23]. If cancer is found at surgery, yearly surveillance should be continued for at least 3 years to assess for the development of new cancers. As with single PSNs that are 8–10 mm, a PET scan should be done before surgery in order to optimize pre-operative assessment[25].

Conclusion

Continuous improvements in CT technology have led to a radical increase in the detection of incidental pulmonary nodules, including SSNs. The new Fleischner Society guidelines outline recommendations for the follow-up and management of these incidental SSNs, many of which represent preinvasive or early invasive primary lung adenocarcinomas. For small GGNs, there is a low likelihood of invasive disease and conservative management consisting of CT surveillance should be used. On the other hand, larger nodules and those with solid components are more suspicious for invasive malignancy and a more aggressive treatment should be considered.

Conflict of interest

The authors have no conflicts of interest to declare.

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