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CHEST IMAGING

PICTORIAL ESSAY

A new classification of adenocarcinoma: what the radiologists need to know

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ABSTRACT

The International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society recently introduced a new classification of lung adenocarcinoma addressing the latest advances in oncology, molecular biology, pathology, radiology, and surgery of lung adenocarcinoma. In this classification, new uniform terminology and diagnostic criteria are described, including the introduction of adenocarcinoma *in situ* as a second preinvasive lesion, as well as the concept of minimally-invasive adenocarcinoma and new subtyping of invasive adenocarcinomas stratified according to predominant patterns. In addition, the previously widely-used term bronchioloalveolar carcinoma is no longer considered valid and has been recategorized. This classification also provides, for the first time, guidance for small biopsies and cytology specimens. This new classification has profound implications for radiology, as much investigation will be needed to correlate these newly introduced concepts (such as histologic subtypes) with radiologic features. Understanding the newly described concept of minimally-invasive adenocarcinoma will be essential in determining sublobar resection for adenocarcinomas. In this manuscript, we briefly review the new classification of lung adenocarcinoma and discuss its radiologic relevance to the reporting, biopsy, and future studies of adenocarcinoma.

Key words: • *lung cancer* • *adenocarcinoma* • *X-ray computed tomography*

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Lung adenocarcinoma classification is an issue of major importance as the adenocarcinoma is the most common histologic subtype of lung cancer in most countries (1). Since the introduction of Noguchi's classification (2), studies have examined the radiologic-histologic correlations of lung adenocarcinoma (3–6). We have seen that persistent ground-glass nodules (GGNs) on computed tomography (CT) have a good correlation with lung adenocarcinoma, from atypical adenomatous hyperplasia (AAH) to invasive adenocarcinoma (3, 5, 6). Studies have also shown that GGNs have a greater likelihood of malignancy than solid nodules at screening CT (3), represent the lepidic component of adenocarcinoma on histology (5), and indicate a better prognosis in patients with lung adenocarcinoma (4, 7). Thus, understanding the significance of GGN in lung adenocarcinoma has allowed the radiologists, pulmonologists, and surgeons to better predict the histologic subtype of adenocarcinomas and consequently to improve the patient's prognosis and care by assisting in decisions regarding surgical intervention or follow-up.

Recently, a new classification of lung adenocarcinoma has been introduced by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society (8). This classification addresses recent advances in oncology, molecular biology, pathology, radiology, and surgery of lung adenocarcinoma. It further provides uniform terminology and diagnostic criteria, as well as guidance for small biopsies and cytology specimens, and multidisciplinary strategic management of tissue for molecular and immunohistochemical studies that more accurately reflect the current understanding of this disease (8). Specific changes in this classification include the addition of adenocarcinoma *in situ* (AIS) as a second preinvasive lesion, and minimally-invasive adenocarcinoma (MIA), and a new stratification of the subtypes of invasive adenocarcinomas based on predominant patterns. Furthermore, the previously used term, "bronchioloalveolar carcinomas (BACs)" is no longer considered valid and has been recategorized.

In this manuscript, we reviewed the new classification of lung adenocarcinoma briefly and focused on its radiological implications.

Preinvasive vs. invasive lesions

The new classification introduces a new term, AIS, as a second lung adenocarcinoma preinvasive lesion in addition to AAH. In the preinvasive lesions category, AAH would be equivalent to squamous dysplasia and AIS to squamous cell carcinoma *in situ*. AIS is defined as a localized adenocarcinoma ≤3 cm, which exhibits a lepidic pattern with neoplastic cells along the alveolar structures without stromal, vascular, or pleural invasion (8). AIS replaces BAC, and this classification recommends the discontinuation of its use. In the past, BAC was used to describe a broad

Figure 1. A 46-year-old man with atypical adenomatous hyperplasia (AAH). Thin-section CT scan shows an 8-mm well-defined pure ground-glass nodule *(arrow)* in the right lower lobe. This nodule was confirmed as AAH by wedge resection.

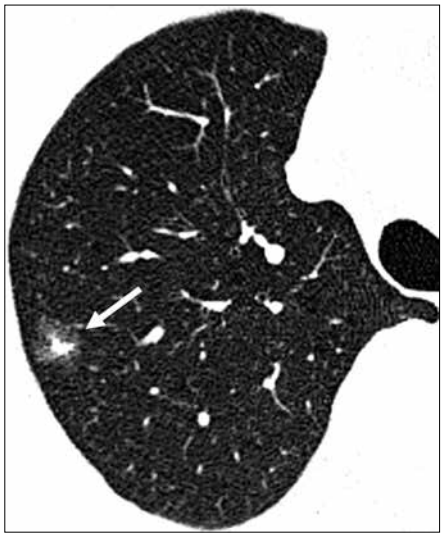

Figure 2. A 55-year-old man with adenocarcinoma *in situ* (AIS). Thin-section CT scan shows a 17-mm part-solid nodule *(arrow)* with lobulated margin in the right upper lobe. The size of the solid portion was 6 mm. This patient underwent lobectomy, and the nodule was confirmed as AIS.

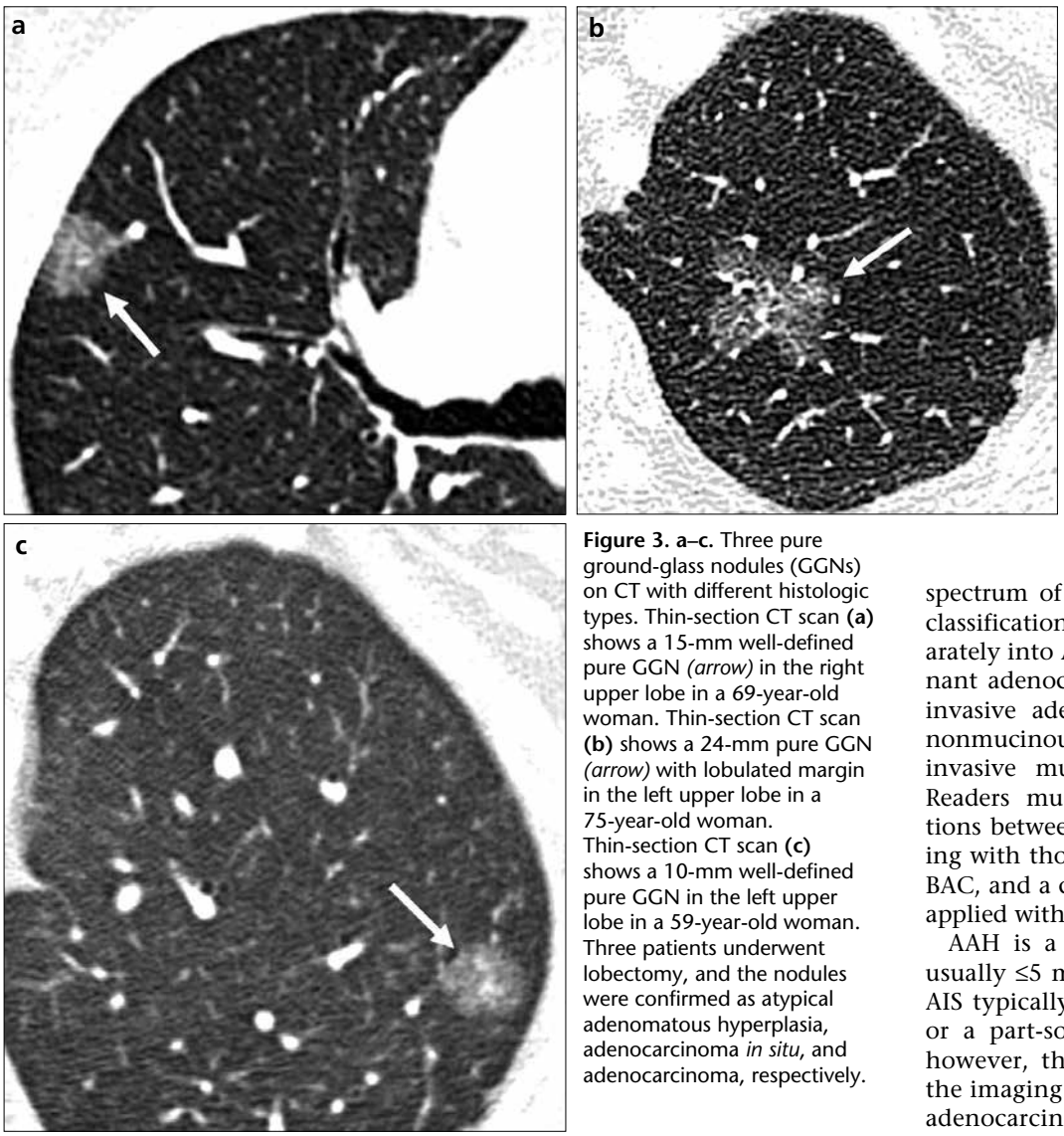

Figure 3. a–c. Three pure ground-glass nodules (GGNs) on CT with different histologic types. Thin-section CT scan **(a)** shows a 15-mm well-defined pure GGN *(arrow)* in the right upper lobe in a 69-year-old woman. Thin-section CT scan **(b)** shows a 24-mm pure GGN *(arrow)* with lobulated margin in the left upper lobe in a 75-year-old woman. Thin-section CT scan **(c)** shows a 10-mm well-defined pure GGN in the left upper lobe in a 59-year-old woman. Three patients underwent lobectomy, and the nodules were confirmed as atypical adenomatous hyperplasia, adenocarcinoma *in situ*, and adenocarcinoma, respectively.

spectrum of tumors, and in this new classification they can be classified separately into AIS, MIA, lepidic predominant adenocarcinoma, predominantly invasive adenocarcinoma with some nonmucinous lepidic component, and invasive mucinous adenocarcinoma. Readers must recognize the distinctions between these terms when dealing with those described previously as BAC, and a clear distinction should be applied within the new classification.

AAH is a faint, pure GGN that is usually ≤5 mm in size (9–11) (Fig. 1). AIS typically presents as a pure GGN or a part-solid nodule (12) (Fig. 2); however, there is an overlap among the imaging features of AAH, AIS, and adenocarcinoma (Fig. 3). Previously,

the main radiologic interest has been the differentiation of benign and malignant GGNs (13), or among AAH, AIS, and adenocarcinoma (6, 14, 15). The differentiation between preinvasive and invasive lesions on CT becomes important in determining patient care, including surgical invention, follow-up strategy, and potential prognosis prediction. By definition, a preinvasive lesion could be considered a candidate for sublobar resection and, a 100% survival rate is obtained with complete resection (16). Until now, the imaging criteria used to distinguish a preinvasive from an invasive lesion have not been clearly established.

Minimally-invasive adenocarcinoma

A certain subset of focally invasive adenocarcinomas (17–19) and AIS (2, 20–22) have shown 100% disease-free survival with complete resection. Therefore, the new concept of MIA has been introduced in the new classification. MIA is a solitary adenocarcinoma ≤3 cm, with a predominantly lepidic pattern and an invasive component ≤5 mm in its greatest dimension (8). In order to classify the lesion as MIA if more than one invasive focus is present, the largest focus must be 5 mm or less in its greatest dimension (8). The invasive component includes histological subtypes other than a lepidic pattern and tumor cells infiltrating myofibroblastic stroma. In cases with invasion to lymphatics, blood vessels, or pleura, or in cases with tumor necrosis, a diagnosis of MIA is excluded. Due to their excellent prognosis, MIA and AIS could be considered candidates for sublobar resection (23–25); however, when considering sublobar resection for MIA differentiating between MIA and invasive adenocarcinoma is important. Since a firm diagnosis of MIA requires thorough histologic sampling of the tumor, it may be difficult to determine the presence, or precisely measure the extent, of the invasive component on a frozen biopsy specimen. Therefore, CT may play an important role in preoperatively predicting the extent of the invasive component in adenocarcinoma. Although the expected CT feature of MIA is a partially-solid nodule with a predominant ground-glass component, the imaging features of MIA have not yet been fully defined (17, 26), and thus require further study.

Invasive adenocarcinoma

Under the 2004 WHO classification, more than 90% of lung adenocarcinomas were classified as mixed-type adenocarcinoma (27). This led to the heterogeneity of mixed-type adenocarcinoma and consequently to difficulty in predicting patient prognosis. To better stratify lung mixed-type adenocarcinoma, the new scheme suggests classification of lung adenocarcinoma according to the most predominant subtype.

In the new classification, invasive adenocarcinoma is present when there is at least one invasive tumor focus measuring more than 5 mm in its greatest dimension (8). Invasive adenocarcinoma consists of lepidic-predominant (formerly non-mucinous BAC pattern), acinar-predominant, papillary-predominant, micropapillary-predominant, and solid-predominant with variants such as invasive mucinous adenocarcinoma, colloid, fetal, and enteric. This approach has facilitated the reliable comparison of histologic results between clinical studies, and has helped to find new correlations between histologic subtypes and both molecular and clinical features (27–30). To-date, the imaging features of adenocarcinoma subtypes have not been well known; thus, discovery of the correlations between predominant patterns and radiologic findings is necessary.

In addition to the concept of a predominant pattern, the introduction of invasive mucinous adenocarcinoma is worthy of note from a radiological perspective. The former term for invasive mucinous adenocarcinoma was mucinous BAC, which has abundant intracytoplasmic mucin. The difference between mucinous AIS and MIA is size >3 cm, a greater than 5 cm extent of invasion, multiple nodules, or the spreading of the nodule into adjacent lung parenchyma with an indistinct border (8). This tumor is usually seen as solid or mostly solid, has frequent air bronchograms, shows a lobar or multilobar distribution, and frequently consists of multiple nodular or consolidative opacities (31–33) (Fig. 4). The CT angiogram sign, which is clear visualization of pulmonary vessels in the areas of consolidation, has also been described for invasive mucinous adenocarcinoma (33) (Fig. 5).

Size of ground-glass nodules

Nodule size-based nodule management is strongly recommended by two guidelines for pulmonary nodules (34, 35) and large screening studies for lung cancer (36, 37), as nodule size may help to determine their growth rate. However, despite its great importance, how nodule size should be measured remains controversial. While unidimensional lesion measurement has been accepted widely, it suffers from high variability and low reproducibility, particularly in smaller lesions, according to a recent study (38). Volume measurements have become possible due to the acquisition of thin-section CT images and advanced dedicated software. Since GGNs have a more indistinct margin than solid nodules, segmentation was performed manually for GGNs, in even the NELSON study (39). Studies that evaluated the variability of volumetry in pure GGNs (40), and those that applied a registration technique to investigate the change of GGNs (41), have demonstrated the potential for the evaluation of GGN growth.

Another issue when measuring GGNs is the question of which is more important to patients' prognosis: lesion size, size of the solid component, or solid proportion. The solid component usually represents areas of fibroblastic proliferation or an invasive component of the tumor, which increases the probability of lymph node metastasis (5). Thus, the size of the solid component could be a prognostic factor; however, the solid proportion remains significant. Kakinuma et al. (42) reported that the vanishing ratio method proved to be a more accurate predictor of five-year relapse-free survival than lesion length or area. The vanishing ratio is the percentage of a lesion's area that is not seen at thin-section CT when comparing images with mediastinal and lung window settings (42).

Since prognosis in terms of the dimensions of the solid component is not yet well-established, the size of both the entire lesion and solid component should be considered for partially-solid nodules. This suggests that the size T factor should be limited to the invasive solid component for adenocarcinomas manifesting as GGNs. CT-pathologic correlations can help determine the appropriate threshold

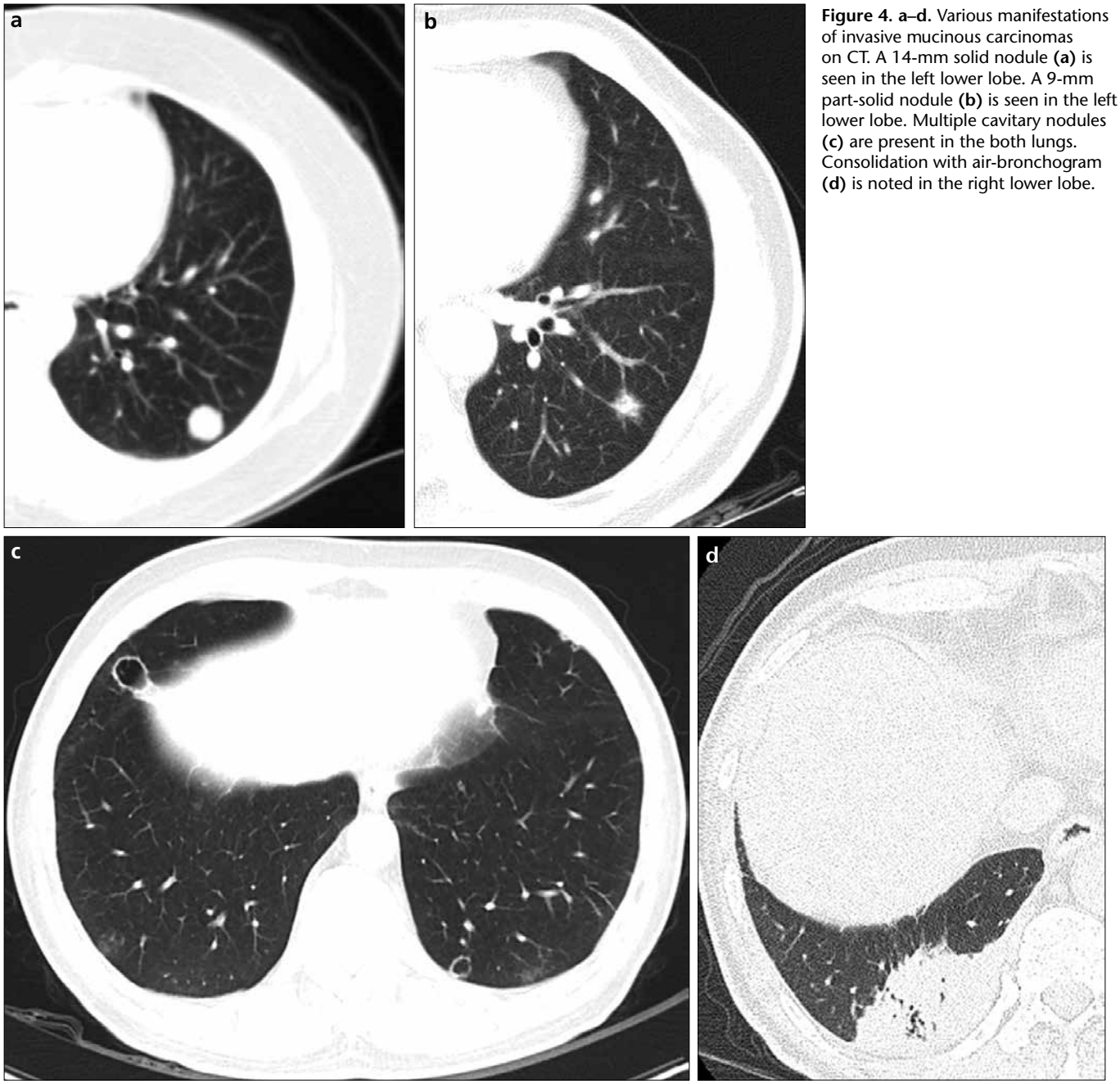

Figure 4. a–d. Various manifestations of invasive mucinous carcinomas on CT. A 14-mm solid nodule **(a)** is seen in the left lower lobe. A 9-mm part-solid nodule **(b)** is seen in the left lower lobe. Multiple cavitary nodules **(c)** are present in the both lungs. Consolidation with air-bronchogram **(d)** is noted in the right lower lobe.

for the invasive component of adenocarcinoma, and therefore can help establish a preoperative plan for sublobar resection in cases of MIA.

Small biopsy or cytology criteria

Approximately 70% of lung cancers are diagnosed in small biopsies and cytology specimens. This classification provides the first guidance for such samples (43). Furthermore, there is an increased need to differentiate adenocarcinoma from squamous cell carcinoma and to investigate molecular profiles for specific therapies, such as epidermal growth factor receptor tyrosine kinase inhibitors that can be used even in patients with locally advanced or metastatic disease.

Biopsy for pulmonary lesions is practiced routinely by most radiologists. Indeed, many radiologists around the world are well-trained for fine-needle aspiration (FNA) of pulmonary lesions; however, a reliable and sufficient sample is necessary for confident differentiation. This can be achieved through coaxial core biopsy, which allows multiple large samplings. GGNs are also good candidates for coaxial core biopsies as they have a diagnostic accuracy of 93.0% (44). A CT-guided coaxial core biopsy can target the solid component of GGNs and can be performed under the guidance of CT (45) or C-arm cone-beam CT (46) without or with little probability of severe complications such as procedure-related death.

Multiple ground-glass nodules

Multiple GGNs in a patient are encountered frequently in clinical

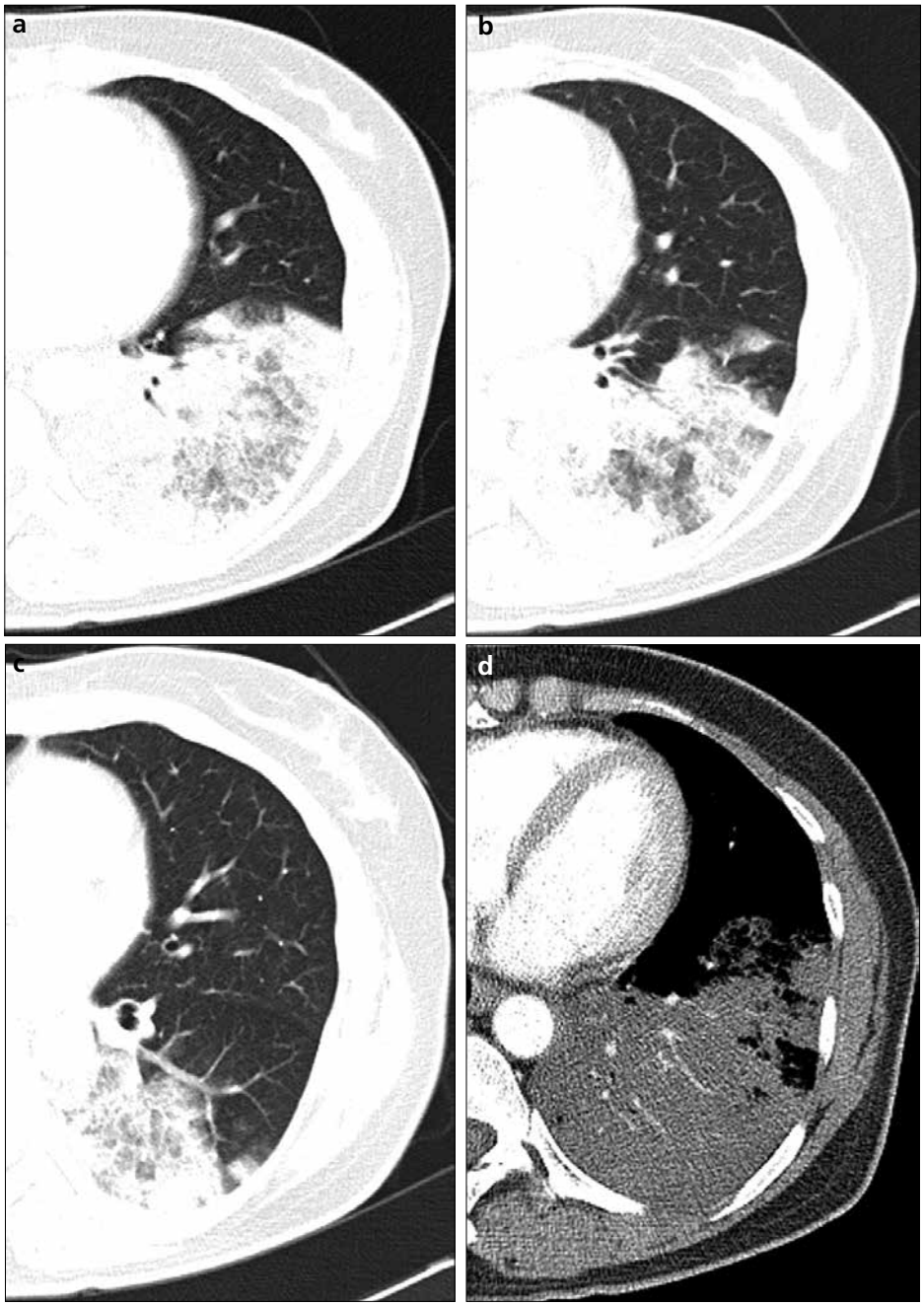

Figure 5. a–d. CT angiogram of the invasive mucinous carcinoma manifesting as lobar consolidation on CT. CT **(a–c)** shows consolidation with ground glass opacity and interlobar septal thickening in the left lower lobe in a 59-year-old female. Pulmonary vessels in the consolidation **(d)** are well-visualized on CT angiogram. She underwent lobectomy and was diagnosed as an invasive mucinous carcinoma.

practice. Recent studies (47, 48) have shown that most of the small, node-negative multiple carcinomas probably represent multiple primaries rather than intrapulmonary metastasis. Thus, multiple GGNs are not contraindication for surgical intervention.

The standard treatment for multiple lesions has not yet been established. Godoy and Naidich (35) suggested that one, or a few dominant lesions, larger than 10 mm or part-solid nodules, can be indicators of surgical intervention, especially limited resection. At follow-up, it is reasonable that similar guidelines to solitary GGNs should be applied for multiple GGNs, given that multiple GGNs are independent, primary tumors. In this context, Kim et al. (49) compared multiple GGNs with solitary GGNs and reported that the two nodule types can probably be followed-up and managed similarly because of their similar prognoses. To confirm these results, prospective follow-up studies are needed.

Management of subsolid nodules

Recently, studies have suggested interim guidelines for subsolid nodules according to nodule size and type (7, 35). These guidelines have suggested that isolated pure GGNs smaller than 5 mm in size do not need follow-up CT studies, pure GGNs of 5 mm or larger require at least an initial follow-up CT at 3–6 months to confirm persistence, and continued follow-up for persistent GGNs of more than two years is recommended. Pure GGNs with overt growth, or a new overt solid portion

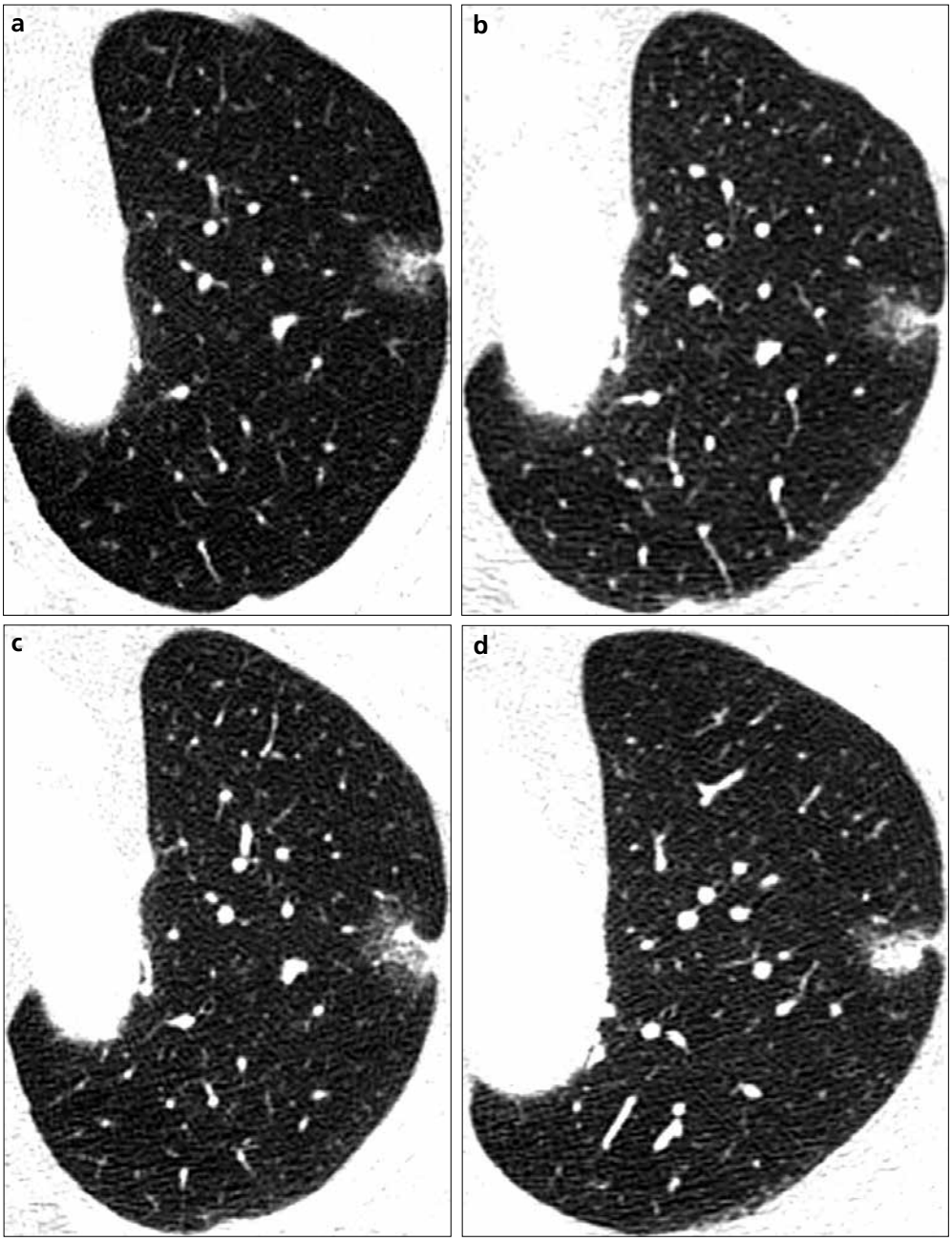

Figure 6. a–d. Progression of part-solid nodule at follow-up CT scans. Initial thin-section CT scan **(a)** shows a 10-mm part-solid nodule in the left upper lobe in a 74-year-old man. After 10 months, follow-up CT **(b)** shows no significant interval change of the nodule in the left upper lobe. Another follow-up CT **(c)** was obtained 34 months later. The part-solid nodule increased in size up to 22 mm. The internal solid portion **(d)** increased in size and extended into the lower portion of the nodule. The patient underwent lobectomy, and pathologic result was adenocarcinoma.

and persistent part-solid GGNs should be resected (Fig. 6). In cases of multiple GGNs, patients can be managed through limited surgical resection for dominant lesions. For accurate evaluation of GGNs, use of thin-section CT acquisition (slice thickness ≤2.5 mm) is essential (50).

The role of transbronchial or transthoracic biopsy in GGNs is limited because a definitive histologic diagnosis cannot be given due to sampling error, or surgical resection may be performed regardless of biopsy results. Thus, transbronchial or transthoracic biopsy should ideally only be performed in patients who are either marginal or poor candidates for surgery, surgical candidates for whom proof of malignancy is still considered necessary, or who present with multifocal disease (51).

The new lung adenocarcinoma classification provides insight into the management of GGNs by introducing the concept of MIA. In addition to AIS, which is the second preinvasive lesion, MIA can be managed more conservatively or with limited resection, especially in aged patients or patients with co-morbidity, due to their excellent prognosis and slow growth rate. Therefore, radiological differentiation of MIA and invasive adenocarcinoma is of major importance. To that end, future studies of the natural history, imaging features, and surgical treatment of MIAs are vital.

Conclusion

The new lung adenocarcinoma classification applies the most recent advances in the understanding of lung adenocarcinomas to make clearer distinctions among lung

Table. Histologic subtypes of adenocarcinoma and CT findings

Histologic subtypes	CT findings
Preinvasive lesions	
Atypical adenomatous hyperplasia	Faint pure GGN usually ≤5 mm in size
Adenocarcinoma in situ	Pure GGN or part-solid nodule
Minimally invasive adenocarcinoma	Unknown
Nonmucinous	
Mucinous	
Invasive adenocarcinoma	
Lepidic predominant	Part-solid nodule or solid nodule
Acinar predominant	Solid nodule
Papillary predominant	Solid nodule
Micropapillary predominant	Unknown
Solid predominant with mucin production.	Solid nodule
Variants of invasive adenocarcinoma	
Invasive mucinous adenocarcinoma	Part-solid nodule or solid nodule or consolidation

GGN, ground-glass nodule.

adenocarcinomas. In this new classification scheme, the term BAC is replaced by AIS as a second preinvasive lesion. MIA is also introduced for a subset of patients with an excellent prognosis and that differ from patients with invasive adenocarcinoma. The new scheme also suggests classification according to the most predominant subtype in order to better stratify mixed-type lung adenocarcinoma. We summarized the imaging features of adenocarcinoma and its histologic subtypes in Table. This classification also, and for the first time, features guidance for small biopsies and cytology specimens.

For radiologists, consistent effort will be required to find imaging biomarkers that can differentiate AAH, AIS, MIA, or lepidic predominant adenocarcinoma and thus facilitate more tailored and uniform management of patients with early lung cancers manifesting as GGNs.

Conflict of interest disclosure

The authors declared no conflict of interest.

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