THE NEW CLASSIFICATION OF LUNG ADENOCARCINOMAS: IMPLICATIONS FOR PATHOLOGISTS AND RADIOLOGISTS*

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The present manuscript is a summary of two lectures which were given respectively by B. Weynand and G.R. Ferretti. The new classification of lung adenocarcinomas has changed the view of the radiologists and the pathologists especially regarding the former bronchiolo-alveolar carcinoma (BAC). The aim of this paper is to correlate radiological and histopathological images according to the 2011 classification for lung adenocarcinoma proposed by the International Association for the Study of Lung cancer, the American Thoracic Society and the European Respiratory Society and to draw attention to the way these lesions can be approached preoperatively.

Key-word: Lung neoplasms.

Lung cancer is very frequent, being the second most frequent tumour in men and the third most frequent in women in Belgium with a very high mortality rate (1). Adenocarcinoma is nowadays the most often diagnosed subtype representing between 35 and 40% of all lung cancers (2). Subtyping may be difficult especially on small specimen such as cytological material from endobronchial ultrasound guided fine needle aspiration (EBUS) and small biopsy fragments, representing 85% of the available diagnostic material. Yet, treatment strategies have changed dramatically over the last decade asking for a precise diagnosis.

In February 2011, the International Association for the Study of Lung cancer, the American Thoracic Society and the European Respiratory Society published a multidisciplinary classification of lung adenocarcinoma involving chest physicians, oncologists, thoracic surgeons, pathologists, molecular biologists and radiologists (3).

It is also well known that there is a close relationship between pathological and CT findings especially for adenocarcinomas which tend to be peripheral lesions (4). Therefore, it seemed interesting to detail the new classification of adenocarcinoma which has been largely accepted by pathologists on insisting on the CT/ histopathological correlations.

The new classification of lung adenocarcinoma: pathological aspects

In the new classification (3), a distinction was made between the reporting of small tissue fragments and cytology and resection specimen. The most important changes which have been implemented concern bronchiolo-alveolar carcinoma (BAC). In the 2004 WHO classification (5), the only distinction used for these tumours was their cell composition, namely mucinous, non-mucinous and mixed BAC. Although it was considered to be of rather good prognosis, this could not always be verified, because its definition was not straightforward and a matter of debate between pathologists. In the new classification, the term BAC has been discarded and replaced by different entities from non-invasive to frankly invasive tumours with different outcomes.

Preinvasive lesions

Atypical adenomatous hyperplasia (AAH) is an entity which has been recognized in the early nineties as being a precursor lesion of adenocarcinoma (6). It is by definition a small lesion measuring less than 5 mm. Usually it is an incidental finding on resection specimen in the vicinity of a larger tumour, not detected before surgery. It is characterized by atypical hyperplastic pneumocytes lining preexisting alveolar septae without any sign of invasion (Fig. 1A,B).

Adenocarcinoma in situ (AIS), which can be nonmucinous or mucinous, is first defined by its size, less than 3 cm. It is rare, representing 3 to 4% of all non small cell carcinomas (NSCLC). It has a 100% 5 year survival. By definition, no invasion is described neither of stroma, vessels nor of pleura, although septal widening is frequent (Fig. 1C,D).

Invasive tumours

Minimally invasive adenocarcinoma (MIA) measures also less than 3 cm, but in contrast to AIS, it harbors an invasive area measuring less than 5 mm composed of any subtype of adenocarcinoma beside lepidic aspect (see further). No invasion of blood vessels, lymphatics or pleura is seen and necrotic areas are not present. It is usually a solitary and discrete tumour, but synchronous tumours can occur. Most of the tumour shows tumour cells growing along alveolar walls centered on a small area of consolidation where infiltrating tumour cells are recognized (Fig. 1E,F). Again, a near 100% 5-year survival is associated with this tumour.

Beside the classical forms of invasive adenocarcinomas, such as acinar, papillary, micropapillary and solid tumours, which present radiologically as solid nodules, two other forms are newly described. Lepidic predominant adenocarcinoma is on the contrary to MIA associated with invasion of blood vessels, lymphatics or pleura and/or necrosis and/or an infiltrative area of more than 5 mm. It is exclusively composed of nonmucinous tumour cells (Fig. 1I, J,K). It is associated with a 90% 5-year survival. Finally, invasive mucinous adenocarcinoma is the last category considered here. It measures more than 3 cm with an invasive area of more than 5 mm. Usually, this tumour is composed of multiple nodules which lack circumscription and shows a miliary spread towards the adjacent lung parenchyma. The tumour is composed of mucinous cells growing along alveoli secreting an abundant amount of mucus filling alveoli (Fig 1G,H). Because of size and multiplicity of localization it is considered to harbor an infiltrating area.

CT/ histopathological correlations: radiological aspects

Radiological definitions

The increasing use of thoracic high resolution multidetector CT
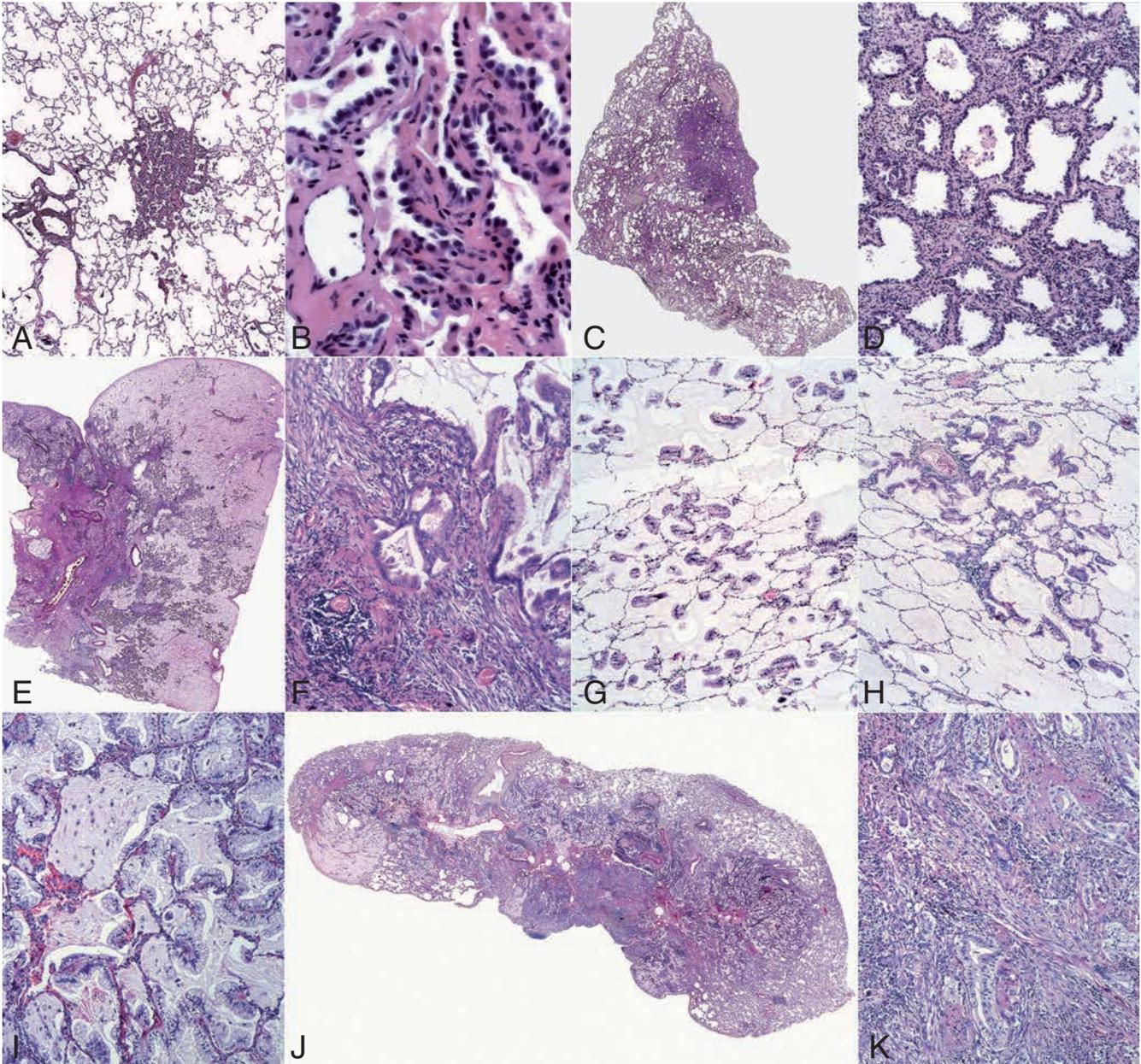
Fig. 1. — A,B: AAH. A: small area of septal widening lined by a few atypical pneumocytes (H&E, bar = 100 μm), B: higher magnification highlighting the atypical pneumocytes (H&E, bar = 10 μm); c,d: AIS. C: larger area of septal widening without invasion (H&E, bar = 5 mm), D: on higher magnification, the enlarged septae are lined by tumour cells (H&E, bar = 50 μm), E,F: MIA. E: low magnification showing whole lesion with a fibrous scar on the left (H&E, bar = 5 mm), F: on higher magnification, a few neoplastic glands are identified in the fibrous area (H&E, bar = 20 μm); G,H: invasive mucinous adenocarcinoma, numerous mucin secreting tumour cells grow along preexisting alveolar septae (H&E, bar = 20 μm); I,J,K: invasive lepidic adenocarcinoma. I: high magnification of lepidic aspect of the tumour (H&E, bar = 20 μm), J: low magnification of whole lesion showing a fibrous area in lower center with a neoplastic glandular infiltration and a periphery characterized by a lepidic growth pattern (H&E, bar = 5 mm), K: invasive acinar adenocarcinoma in the fibrous scar (H&E, bar = 20 μm).

(HR-MDCT) in clinical practice and for lung cancer screening purposes have allowed performing correlations between histopathological presentation of adenocarcinoma and radiological patterns. Three types of pulmonary nodules (by definition rounded or irregular opacity ≤ 30 mm in diameter) are defined on HR-MDCT (7):

1. subsolid nodules that include
   a. *Nonsolid nodules* (Fig. 1, 2) also called pure ground-glass nodules), which are spherical or oval pulmonary nodules of hazy increase of lung attenuation, with preservation of vascular structure visualization.
   b. *Part-solid nodules* (Fig. 3, 4) also called mixed ground-glass nodules) that have a nonsolid component containing tissue density (or solid) component(s) with soft tissue density completely obscuring the lung parenchyma and the contour of the vessels with which it is in contact. Solid component can be either located centrally, peripherally or forming several islets (8).

2. Solid nodules (Fig. 5, 6) which are focal areas of increased attenuation of lung parenchyma that obscure any normal structure such as vessels without any ground glass opacity.

Although close but imperfect correlations exist between HR MDCT patterns of pulmonary nodules and pathology of adenocarcinoma, radiologist should remember that all these patterns may also be caused by benign conditions such as infectious pneumonia, organizing pneumonia, localized area of fibrosis and inflammation (9, 10).

CT/histopathological correlation (Table I)

Atypical adenomatous hyperplasia (AAH) always appears as nonsolid nodule (11). AAH is a pure GGO nodule measuring ≤ 5 mm, but can exceed 10 mm. AAH can be solitary but is often multiple and bilateral.

Adenocarcinoma in situ (AIS), usually appears on HR-MDCT as a pure GGO nodule > 5 mm, but may present as a part solid or rarely as a solid nodule. Part solid or solid presentations have been correlated to alveolar collapse (12) or rare mucinous types. A recent case report showed that gravity may increase artificially the density of pure GGO nodules located in the posterior lung zones transforming the GGO presentation into a solid one. CT in prone position is suitable in order to demonstrate the GGO pattern (13). Criteria have been studied in order to differentiate AIS from AAH within GGO nodules: AIS tends to present with a bubble like pattern and a higher attenuation, diameter is larger (> 5 mm) than AAH. However, these criteria suffer many exceptions and there is an overlap among imaging patterns of AAH, AIS, and MIA.

MIA has been described more recently and extensive correlations are lacking. However, the majority of MIA is nonmucinous and appears as part solid GGO nodule, with a solid portion of less than 5 mm (14). Mucinous MIA is very rare and may appear as solid nodules.

Invasive adenocarcinomas are not always solid nodules and their CT appearance is related to their histopathological pattern. Invasive adenocarcinoma with predominant lepidic pattern tends to present as part solid nodule or solid nodule but rarely as pure GGO nodule. There is a correlation between the solid part of the nodule being the invasive component at histology and the GGO being the lepidic component. Tumour aggressiveness increases as the solid part becomes more prominent in the nodule, resulting in a reduction in tumour volume doubling time, an increase in frequency of lymph node
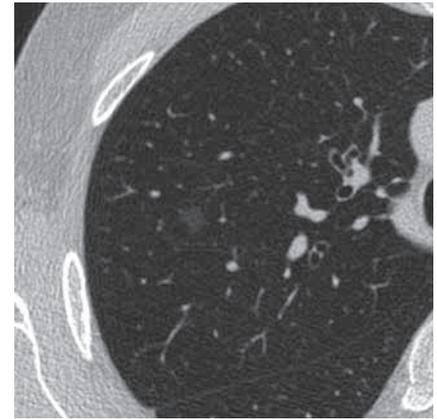
Fig. 2. — AAH in a 52-year-old woman presenting as a pure ground glass opacity nodule, 7-mm in diameter in the right upper lobe.

metastases and vascular invasion, and an increase in risk of local recurrence (15, 16, 17). In clinical practice, radiologists should estimate the relative proportion of the solid part in a mixed GGO as it showed a prognostic value.

Other types of invasive ADC more often present as solid nodules and are associated with a more severe prognosis.

Invasive mucinous adenocarcinoma (Fig. 7) has replaced the term "mucinous BAC". The HR MDCT presentation of these tumours can be

Table I. — 2011 IASLC/ATS/ERS classification of lung adenocarcinoma in resection specimens.

	IASLC/ATS/ERS classification	Former denomination (WHO 2004)	HRCT usual pattern
Preinvasive lesions	Atypical adenomatous hyperplasia (AAH)	AAH	Pure GGO ≤ 5 mm
	Adenocarcinoma in situ (AIS) (≤ 30 mm)	Solitary BAC	Pure GGO ≤ 30 mm (Rarely part solid GGO or solid)
Minimally invasive lesions	Minimally invasive adenocarcinoma (MIA) (≤ 30 mm lepidic predominant with invasion (≤ 5 mm)	ADC mixed subtype with predominant BAC pattern	Pure GGO Part solid GGO solid
Invasive lesions	Lepidic predominant Acinar predominant Papillary predominant Micropapillary predominant Solid predominant	Nonmucinous BAC with invasion > 5 mm	Part solid GGO Solid
Variants of invasive lesions	Invasive mucinous ADC Colloid Fetal Enteric	Mucinous BAC	Part solid GGO / solid Consolidation
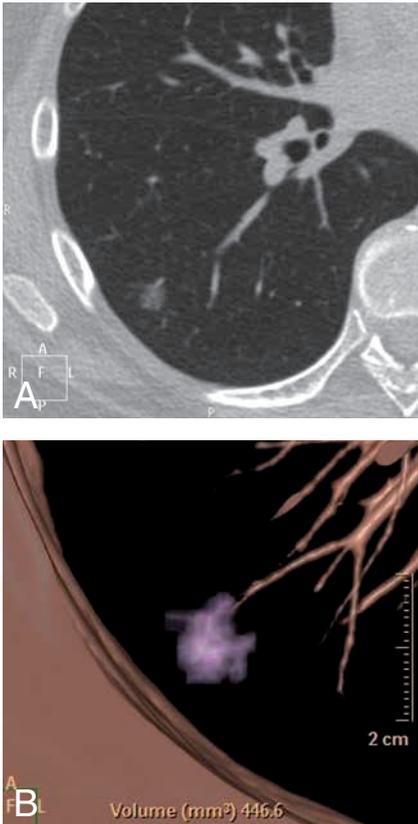
Fig. 3. — AIS in a 66-year-old woman presenting as a pure ground glass opacity nodule, 9.5-mm in diameter in the right lower lobe. A: HR CT. B: 3D volume assessment of the lesion estimated at 447mm³.

very different from one patient to another as it comprises chronic pulmonary consolidations with air bronchogram and angiogram, mutifocal unilateral or bilateral consolidations, nodules, or masses of solid, non solid or sub solid appearance, that have a bronchogenic distribution (18).

CT technical considerations

Detection and characterization of lung nodules is optimized by using HR-MDCT as compared to conventional slice by slice CT or helical CT with thick collimation and should therefore be used in clinical practice (19). Low dose technique is adapted to detect pulmonary nodules while reducing patient's exposure to radiation. However, dose length product associated with HR MDCT can vary considerably according to the patient's morphology, the technology of acquisition and the use of iterative reconstruction. Therefore, no recommended value can be formulated but the principle of ALARA *(As Low As Reasonably Achievable)* should be respected. Contrast media
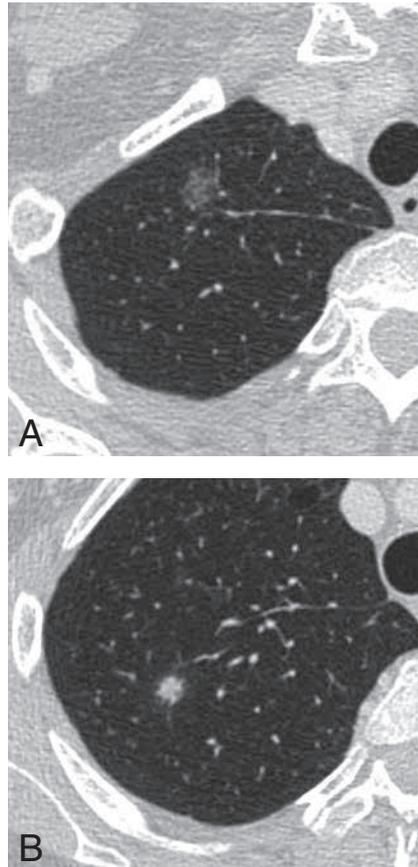
Fig. 4. — 66-year-old woman former smoker presenting with 2 pulmonary nodules in the right upper lobe. Treatment consisted in right upper lobectomy. A: pure GGO nodule, 13-mm in diameter, identified histologically as nonmucinous AIS. B: mixed nodule, 9-mm in diameter, with GGO < 10% surrounding the solid part, related to nonmucinous AIS with centrally located fibrosis responsible for the solid pattern at CT.

injection is not useful to detect or characterize pulmonary nodules in clinical practice but it is useful to establish the extent of the tumour (N and M of the TNM classification). Follow-up of small pulmonary nodules should be optimally performed with the same CT scan unit and same exam protocol in order to reduce technical variations that may increase the level of errors in measurement, density evaluation, and volume calculation of nodules. Standardization of acquisition parameters is mandatory to follow pulmonary nodules.

Evolution of the nodules

Repeated CT scans have allowed assessment of the natural history of nonsolid and part solid nodules as compared to solid ones. Three types of morphological development for
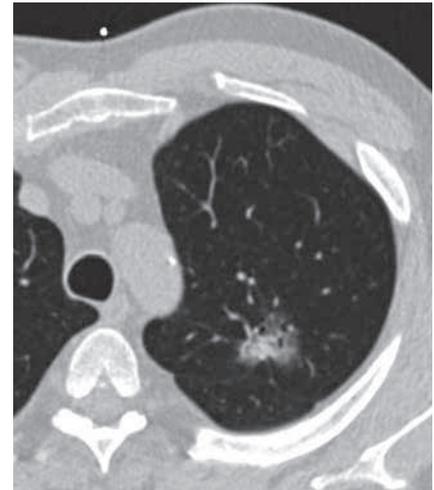
Fig. 5. — Invasive acinar adenocarcinoma in a 61-year-old man smoker. Partly solid nodule, 25-mm in diameter, in the left upper lobe. Notice the air-bronchogram and the retraction of the main fissure.

Fig. 6. — Invasive papillary ADC, T1aN0 in the right upper lobe in a 54 -year-old man smoker. CT shows solid nodule with irregular and speculated contours.

malignant nonsolid nodules were described in a small series (20): increase in size of the nonsolid area (n = 5); reduction in size of the nonsolid area coupled with appearance of a solid component (n = 2); stable dimension of the nodule but progression from non-solid to a part-solid nodule (n = 1).

The doubling time of malignant solid nodules is usually between 30 and 400 days. Doubling time of pre-invasive or invasive nonsolid or part-solid nodules is longer and has been
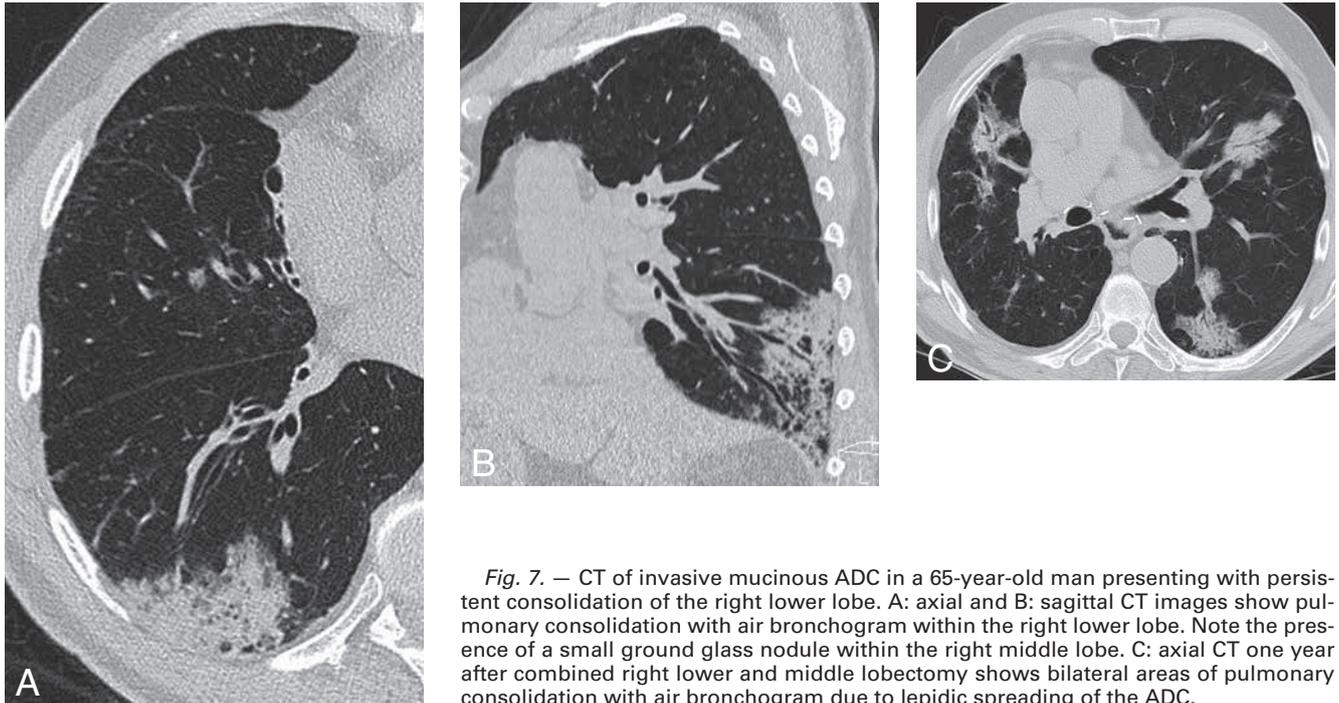
Fig. 7. — CT of invasive mucinous ADC in a 65-year-old man presenting with persistent consolidation of the right lower lobe. A: axial and B: sagittal CT images show pulmonary consolidation with air bronchogram within the right lower lobe. Note the presence of a small ground glass nodule within the right middle lobe. C: axial CT one year after combined right lower and middle lobectomy shows bilateral areas of pulmonary consolidation with air bronchogram due to lepidic spreading of the ADC.

calculated at 813 +/- 375 days for nonsolid nodules, 457 +/- 260 days for part-solid nodules, and only 149 +/- 125 days for solid nodules (21).

Because of the long doubling times, prolonged surveillance of nonsolid and part-solid nodules is recommended; this goes against the concept of 2-year nodule stability implying that a nodule is benign (22).

Transthoracic biopsy: implications for radiologists

Image guided percutaneous needle biopsy is a valuable technique to provide cytological or histological samples allowing for tissue characterization, as well as immunohistochemical and molecular analysis, when indicated. Such variety of analysis permits classifying precisely lung tumours into small cell carcinoma or non small cell carcinoma, and the new classification emphasizes that NSCLC be classified into precise subtypes such as adenocarcinoma or squamous cell carcinoma. In case of metastatic adenocarcinoma, genotyping the tumour opens the way to personalized therapy using new drugs, such as tyrosine kinase inhibitors in case of epidermal growth factor receptor (EGFR) mutation. Due to the increasing demand of tissue for performing all these analysis, radiologists should be aware that they should provide as much tissue as possible from transthoracic biopsies

and preserve the specimen according to multidisciplinary group recommendations in order to optimize the use of these samples (23).

However, due to the heterogeneity of subsolid nodule, the diagnosis of AIS and MIA requires that the entire lesion be analyzed by the pathologist on a surgical resection, therefore transthoracic biopsy is not recommended in these nodules.

PET evaluation of subsolid pulmonary nodules

PET is not recommended in order to characterize pure GGO nodules as it has demonstrated a low sensitivity to depict AIS or MIA, related to the low metabolism of preinvasive or minimally invasive adenocarcinoma with lepidic pattern. Moreover, these tumours are localized and are not associated with node or distant metastases. On the contrary PET is indicated in part solid nodules in which the solid portion is > 10 mm, according to the recently published guideline of the Fleischner society (24).

Recommendations for managing non solid nodules

After the propositions of Godoy and Naidich (19), the Fleischner society recently published recommendations adapted to the specific situation related to the discovery of

subsolid nodules, completing the 2005 recommendations for solid nodules (24).

Specific recommendations for pathologists and radiologists proposed by the IASLC/ATS/ERS classification of lung adenocarcinoma (3)

1. the term bronchiolo-alveolar carcinoma (BAC) should be avoided to describe a pure GGO or part-solid nodule with < 50% GGO. These tumours should be classified as AAH, AIS, MIA, although precise correlations between CT and pathology for MIA are lacking.

2. invasive adenocarcinoma appears usually as a solid nodule, as a part solid nodule or infrequently as pure GGO

3. morphological criteria are associated with well differentiated localized stage IA adenocarcinoma and longer volume doubling time when cystic or bubble like lucencies are present within a pure GGO nodule.

4. the presence of spiculation or peribronchovascular thickening around the nodule is associated with vascular invasion and lymph node involvement and poorer prognosis.

5. small peripheral adenocarcinomas with a nonsolid component of over 50% on CT present significantly less lymph node metastases or vascular invasion than those with a nonsolid component of less than 10%.

The nonsolid proportion influences patients survival as it was significantly superior in patients presenting a nodule with a nonsolid component of > 50% compared to those with a nonsolid component of < 50%.

6. As size is a very important criterion for the differential diagnosis of all these lesions, it is critical that it is recorded correctly, on thin-section CTs. Therefore, pathologists and radiologists are advised to record not only the total area of the tumour, including the ground-glass component, but also the solid part, separately. This will help in identifying in the future if invasive size predicts prognosis better than total size.

In conclusion, in order to standardize terminology, the new IASLC/ATS/ERS classification of lung adenocarcinoma should be used by all the specialists involved in lung cancer care because it results from a multidisciplinary approach and takes into account the most recent developments in the field of clinical, histopathological, molecular, radiological and surgical research. With better knowledge of the CT/histopathological correlations, pretreatment diagnosis will be more and more accurate.

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