Review Article

Pulmonary ground-glass opacity: computed tomography features, histopathology and molecular pathology

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Abstract: The incidence of pulmonary ground-glass opacity (GGO) lesions is increasing as a result of the widespread use of multislice spiral computed tomography (CT) and the low-dose CT screening for lung cancer detection. Besides benign lesions, GGOs can be a specific type of lung adenocarcinomas or their preinvasive lesions. Evaluation of pulmonary GGO and investigation of the correlation between CT imaging features and lung adenocarcinoma subtypes or driver genes can be helpful in confirming the diagnosis and in guiding the clinical management. Our review focuses on the pathologic characteristics of GGO detected at CT, involving histopathology and molecular pathology.

Keywords: Ground-glass opacity (GGO); computed tomography (CT); pathology; driver genes; epidermal growth factor receptor gene (*EGFR*); anaplastic lymphoma kinase gene (*ALK*); Kirsten rat sarcoma viral oncogene homolog (*KRAS*)

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Introduction

Pulmonary ground-glass opacity (GGO), is defined as hazy opacity that does not obscure underlying bronchial structures or pulmonary vessels at high-resolution computed tomography (HRCT) (1). The detection and recognition of GGO is based on a subjective assessment of lung attenuation at CT, therefore, CT should be performed within objective parameters that make lesion depiction reliable and reproducible (2). These lesions include both benign and malignant lesions such as focal interstitial fibrosis, inflammation, hemorrhage, or lung adenocarcinoma and their preinvasive lesions (3,4). Many studies have reported that preoperative CT scan findings are related to pathological features and postoperative prognosis (5-7).

Lung adenocarcinoma is the most common histologic subtype of lung cancer and shows high heterogeneity at histology and cellular level (8,9). In 2011, the International Association for the Study of Lung Cancer, American

Thoracic Society, and European Respiratory Society (IASLC/ATS/ERS) have proposed a new classification for lung adenocarcinoma, refining its classification, which emerged into a better standard of clinical treatments (10). This new classification is of stage-independent prognostic and also of high predictive value for adjuvant treatment (11,12) and was most recently incorporated into the new 2015 WHO classification (13). Furthermore, lung cancer and especially lung adenocarcinoma, with specific mutations or rearrangements in genes such as EGFR, KRAS, and ALK, may show different tumor sensitivities to targeted therapeutic agents. Therefore, it is desirable to be aware of the correlations between GGO pattern and pathology subtypes and/or expression of driver genes.

Histopathology and CT features

Pulmonary GGO nodules can be observed in benign conditions, including focal interstitial fibrosis, inflammation, and hemorrhage, as well as in preinvasive lesions such as atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), or in malignancies such as minimally invasive adenocarcinoma (MIA), lepidic-predominant invasive adenocarcinomas (LPA) (10,14).

Focal interstitial fibrosis

Focal interstitial fibrosis represents the main entity among benign GGO (3). At histopathologic analysis, tissue specimens show interstitial septal thickening with fibroblast proliferation and preservation of the intra-alveolar airspace (15); if solid components are present, they may be related to the presence of fibrotic foci and alveolar collapse (16). Although recognized as benign entity, focal interstitial fibrosis shares many CT features with neoplastic diseases, and its differentiation from a malignant lesion is mainly based on its stability over time.

Inflammation

Inflammation showing as GGO, can be related to any kind of infectious pneumonia, but it is a more frequent presentation for cytomegalovirus (CMV) and Pneumocystis jirovecii CT findings of CMV infection may include GGO, dense consolidation, bronchial wall thickening or bronchiectasis, and interstitial reticulation without air-space disease (17); CT findings for Pneumocystis jirovecii infection may include the presence of an isolated ground-glass infiltrate without additional findings in the proper clinical setting (18).

Pulmonary hemorrhage

Pulmonary hemorrhage can be diffuse, patchy, or focal, depending on the underlying cause. Pulmonary-renal syndromes that may cause pulmonary hemorrhage include Goodpasture's syndrome, Wegener's granulomatosis, systemic lupus erythematosus, Henoch-Schonlein purpura, mixed connective-tissue disease, and other vasculitis (14). Other causes of pulmonary hemorrhage include anticoagulant therapies, disseminated intravascular coagulation, thrombocytopenia, leukemia, acute lung injury, aspiration of blood, drug toxicity, traumas, and mitral stenosis (19). CT scans may show consolidation with GGO and interlobular septal thickening, as well as a halo of GGO around a focal area of lung consolidation.

GGO can be observed not only in presence of benign conditions but also in preinvasive lesions or in malignancies.

AAH

AAH is defined as a localized, small usual pneumocytes and/or Clara cells lining the alveolar walls and respiratory bronchioles (20). On chest CT, AAH is characteristically shown as a small pure GGO, usually measuring <5 mm, but a few can reach 12 mm. Lesions may be single or multiple with low density. Several authors have reported that AAH may be a precancerous lesion or a putative precursor of well-differentiated adenocarcinoma of the lung (21).

In 2011, IASLC, ATS and ERS proposed a new classification for lung adenocarcinoma, which is now included in the official 2015 WHO classification, that included a number of changes to previous classifications, which now considers resection specimens, small biopsies, and cytology specimens (10). For resection specimens, the new terms of AIS and MIA are introduced for small adenocarcinomas, which show pure lepidic or predominantly lepidic growth, with invasion ≤5 mm, respectively. Invasive adenocarcinomas are now classified with a newly added semi-quantitative pattern analysis, a micropapillary pattern, except lepidic, acinar, papillary, and solid by their predominant pattern. This classification also provides guidance for biopsies and cytology specimens.

AIS

AIS is a localized small by their predominant pattern. This classification also provides guidance for biopsies and cytology specimen lepidic growth that lack stromal, vascular, or pleural invasion. AIS was defined as a preinvasive lesion. On CT, nonmucinous AIS appears typically as a pure GGO (22). The pure GGO of AIS usually appears on thin-

section CT as slightly higher attenuation compared with the very faint GGO of AAH (23,24). AIS can also be either single or multiple (25).

MIA

MIA is a small, solitary adenocarcinoma (ltiplein-section CT as slight lepidic pattern and invasion carcinoma) (26). A provisional description of nonmucinous MIA on thin section CT is a part-solid nodule consisting of a predominant ground-glass component and a small solid component measuring 5 mm or less (27). Mucinous MIA can appear as a solid or part-solid nodule (28). There is an overlap among imaging features of AAH, AIS, and MIA. MIA was more often a larger, lobulated or irregular, mixed ground-glass nodule with a solid component larger than 5 mm, and a higher attenuation value (29).

LPA

LPA, a subtype of invasive adenocarcinoma, is defined as nonmucinous adenocarcinomas previously classified as a mixed subtype in which the lepidic component is predominant. A diagnosis of LPA rather than MIA can be made if the tumor contains >5 mm of a histologic subtype other than a lepidic pattern (i.e., acinar, papillary, micropapillary, or solid) or >5 mm of myofibroblastic stroma with invasive tumor cells; or invades lymphatics, blood vessels, or pleura; or contains tumor necrosis. Consequently, on CT, it can be shown as a part-solid opacity with variable proportions of ground-glass and solid components (10), usually described as a prevalent GGO nodule, with a solid component >5 mm. In general, other subtypes of invasive adenocarcinomas such as acinar, papillary, micropapillary and solid predominant lesions rarely show GGO at HRCT.

A careful evaluation of the CT features of nodular GGO in neoplastic disease may help in assessing the disease prognosis. Indeed, in a retrospective review, after surgery AAH and AIS had 100% 5-year disease-free survival, respectively; MIA had almost 100% 5-year disease-free survival. The 5-year disease-free survival of invasive adenocarcinoma, as for example when a nodular GGO lesion with a predominant solid portion is accompanied by CT features such as spiculations, pleural retraction, or bronchovascular bundle thickening, is significantly reduced (16), likely because such lesions are associated with higher probabilities of lymph node metastasis and vascular invasion (30). The sub-classification of invasive adenocarcinoma has prognostic import as well, since solid and micropapillary predominant lesions have a poor prognosis, while papillary and acinar adenocarcinoma have an intermediate prognosis and LPA have a favorable prognosis (11).

Currently, only a pathological assessment can ascertain if a GGO is benign or malignant. However, the clinical setting and a careful assessment of changes of the GGO appearance at CT over time, may enable an accurate suggestion of diagnosis. It is indeed known that most benign conditions resolve spontaneously or after appropriate treatment over weeks or months, and patients have characteristic clinical findings and symptoms (14). In contrast, malignant neoplasms are persistent, and their size and attenuation may increase over several months or years, usually in absence of clinical symptoms (14).

For this reason, management of GGO detected at CT for lung cancer screening is usually based on their re-evaluation. In 2016, the National Comprehensive Cancer Network (NCCN) made the latest guidelines (version 1, 2017) for lung cancer screening (31).

For solid nodules: nodules less than 6 mm can only accept ongoing annual screening. On the other hands, if the nodules are in 6 to <8 mm, they are recommended to undergo a repeat low-dose CT in 6 months. If the nodules become stable, repeated at 6 months, and if continued stable, reverting to annual screening. Nodules ≥8 mm are to be considered for PET. If the clinical, radiologic, and PET findings suggest a suspicion of lung cancer, the patients need biopsy or surgical excision. Otherwise, if the nodules are low suspicion for lung cancer, then they would be followed with a low-dose CT in 3 months, and if stable, a follow-up CT 6 months later, and if still stable, reverting to annual follow-up imaging.

For part-solid nodules: nodules less than 6 mm can only accept ongoing annual screening. If the nodules are in ≥6 mm with solid component <6 mm, they are recommended to undergo a repeat low-dose CT in 6 months, and if continued stable, reverting to annual screening. Nodules with solid component ≥6 mm are to be considered for PET. If the clinical, radiologic, and PET findings suggest a suspicion of lung cancer, the patients need biopsy or surgical excision. Otherwise, if the nodules are low suspicion for lung cancer, then they would be followed with a low-dose CT in 3 months. If still stable, nodules with solid component 6 to <8 mm are to be reverting to annual follow-up imaging, and nodules with solid component ≥8 mm are recommended to undergo a repeat low-dose CT in 6 months, and if continued stable, reverting to annual

follow-up imaging.

For non-solid nodules: nodules less than 20 mm are followed simply with routine annual low-dose CT. However, if these nodules have increased in size or have developed a solid or part solid component in follow-up, then they would undergo either escalated interval follow-up low-dose CT in 3 to 6 months, biopsy, or surgical excision. Nodules ≥20 mm are recommended to undergo a follow-up low-dose CT in 6 months. If the nodules become stable, repeated at 6 months, and if continued stable, reverting to annual screening. If they increase in size or become solid or part-solid, then they are recommended to undergo either repeat low-dose CT in 6 months, biopsy, or surgical excision because of the high suspicion of adenocarcinoma or AIS.

In this guidelines, the definition of nodule growth is as follows: (I) for nodules 15 mm or smaller: an increase in mean diameter of 2 mm or more in any nodule or in the solid portion of a part-solid nodule when compared with the baseline scan; or (II) for nodules 15 mm or lager: an increase of 15% in mean diameter when compared with the baseline scan. Mean diameter is the mean of the longest diameter of the nodule and its perpendicular diameter (31). Although this NCCN algorithm is very useful, of course, clinical scenarios should make precise therapeutic regimens of pulmonary nodules according to the actual situation of patients, improving the survival of early lung cancer and diagnosis level.

Molecular pathology and CT features

Recent practice guidelines in oncology and pathology recommend that all locally advanced and metastatic NSCLC with adenocarcinoma histology undergo testing for the most common targetable genetic abnormalities, such as epidermal growth factor receptor gene (*EGFR*) mutations, anaplastic lymphoma kinase gene (*ALK*) rearrangements, and non-targetable such as Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutations (32).

To date, several studies, mostly in Japan, China and Korea, have investigated the association between CT imaging features and driver genes such as *EGFR*, *ALK*, and *KRAS*. Most reports focused on the presence of any GGO or GGO proportion and some of the findings are conflicting. The definition of GGO proportion differs among studies and the following parameters have been used to calculate the GGO proportion: consolidation/tumor dimension ratio (33,34), GGO/tumor area ratio (35), area ratio of tumor on mediastinal windows to that on lung windows, GGO/tumor volume ratio (6,36,37), and the product of the dimension ratio of the tumor on mediastinal windows to that on lung windows to calculate the tumor shadow disappearance rate (TDR) (37-39).

Yano *et al*. (40) demonstrated that *EGFR* mutations were found more frequently in small peripheral adenocarcinoma with a diameter <3 cm and with a GGO ratio ≥50%, especially among women. Sugano *et al*. (33) examined the presence of GGO and *EGFR* mutations in 136 patients with surgically resected primary lung adenocarcinoma. Although no significant association was found between GGO and *EGFR* mutations (P=0.07), the *EGFR* mutation occurred more frequently in male patients with GGO than in those without GGO. Furthermore, two studies (41,42) involving 263 and 285 lung adenocarcinoma, reported that the *EGFR*-mutated group had significantly higher frequencies and no higher frequencies of GGO, respectively. Lee *et al*. (6) found that GGO volume percentage in tumors with L858R mutation was significantly higher than that in *EGFR* wild-type tumors (P=0.0001) and 19 deletion mutated tumors (P=0.0006). A significant trend of prevalence of L858R mutation increasing along with increasing GGO volume percentage (P=0.0001) was found. Discordant to Lee *et al*.'s report, Yang *et al*. did not find a significant correlation of GGO volume ratio with L858R mutation, but with 19 deletions (36), while Hong *et al*. (34) found that GGO ratio in tumors with either exon 19 deletions or L858R mutation, was significantly higher than that in *EGFR* wild-type tumors (P=0.009 and 0.029, respectively). Based on the abovementioned studies, we may assume that the presence of GGO or higher GGO ratio may be associated with higher frequencies of *EGFR* mutation. However, the association between GGO and *EGFR* mutation is still debated because of conflicting results of different studies (39,43-45). These controversial results may be the result of different ethnicity, grouping methods, measurement of GGO ratio, sample size and inclusion criteria among studies.

Besides *EGFR* mutation status, a few studies investigated the association between GGO and *EGFR* copy number or protein overexpression. *EGFR* amplification were inversely correlated with the GGO percentage, indeed the frequency of FISH-positivity increased as the proportion of GGO decreased (6,46,47).

There are limited numbers of reports focusing on *KRAS* mutations or *ALK* rearrangements. Most studies found no significant association between *KRAS* mutations and presence

of any GGO (43,44,48) or GGO ratio (33). One study (45) revealed that *KRAS* mutations were more common in lesions with a lower GGO proportion. Zhou *et al*. (37) compared the radiologic characteristics of lung adenocarcinomas with presence or absence of *ALK* rearrangements and *EGFR* mutations. They demonstrated that the percentages of GGO volume and TDR were significantly lower in the *ALK* rearrangements group than the *EGFR* mutation group and the wild type group, which was consistent with the study by Fukui *et al*. (49). In their analysis, the mean TDRs were significantly lower in the *ALK* rearrangement positive group (P=0.0006). Furthermore, evaluation of imaging findings of 36 cases with advanced *ALK*-positive NSCLC showed a prevalence of solid pattern of growth, without GGO (50). These features might suggest that they have a more invasive nature than those with more GGO components. Generally, ALK rearrangement is rare in lung adenocarcinoma presenting as GGOs and is associated with a more advanced stage and larger tumor size (38).

Concerning the GGO change patterns, Aoki *et al*. (51) evaluated 25 lung adenocarcinomas <3 cm with GGO (>50%): tumor size increased in 19 of 25 adenocarcinomas during the observation period and the GGO changes in 19 patients were classified into four patterns: persistent pure GGO, change from pure to mixed GGO, mixed GGO with growth of solid component, and mixed GGO with growth of GGO component. *EGFR* mutations were found in all four patterns and were not correlated with GGO change patterns. Accordingly, another study (52) involved 23 lung adenocarcinomas and classified patterns of radiological changes into three groups: pure GGO without consolidation; appearance or increase in consolidation within pure GGO; consolidation without pure GGO. There was no trend between *EGFR* mutations and patterns of radiological changes during the follow-up period. Interestingly, both studies reported that inactivation of p53 may be associated with the appearance or growth of central consolidation within pure GGO. In a recent study (53), 104 GGO nodules <3 cm with ground-glass component >50% were evaluated for the presence of *EGFR*/*KRAS*/*ALK*/*HER2* mutations and growth, defined as ≥2 mm increase in diameter or appearance of a solid component. Among the 71 lesions evaluated for growth, *EGFR* mutation was correlated with growth, whereas quadruple-negative tumors were significantly associated with no-growth.

The relationship of gene mutation status and the presence of multiple GGO lesions in lung adenocarcinoma were seldom studied. In 2009, Chung *et al*. (54) examined 56 multiple pulmonary nodules presented as GGO in 24 patients, to assess if the mutation status of EGFR and *KRAS* genes correlates with radiological features. A total of 17 patients showed different *EGFR* gene expression in their multifocal lesions, and only 7 patients had identical gene status without any mutation. *KRAS* gene mutation also showed asymmetric fashion in multiple lesions. Combining both *EGFR* and *KRAS* gene alterations, 75% of the patients had heterogeneous genetic status in their multiple lesions. Two recent studies also reported the heterogeneity among multiple GGOs. One analyzed for mutations in *EGFR*, *KRAS*, *HER2*, *BRAF*, and *PIK3CA* together with fusions in *ALK*, *ROS1*, and *RET*. The discordance rate of driver mutations was 80% in those patients harboring at least one of the detected driver mutations (55). The other (56) focused on subtypes of *EGFR* mutation and reported a discordance rate of 92.1%. These results suggest that multiple GGO lesions in lung adenocarcinoma may have a different origin. However, sequential or multiple biopsies to identify subclones can rarely be implemented in routine clinical care.

Future possibilities of evaluation of GGO: radiomics and liquid biopsies

New tools under consideration for evaluation of lung nodules, including GGO, are radiomics and liquid biopsies.

Radiomics is an emerging field that converts imaging data into a high dimensional mineable feature space using a large number of automatically extracted data-characterization algorithms. These imaging features capture distinct phenotypic differences of tumours and may have prognostic power and thus clinical significance across different diseases (57). Indeed, quantitative image features based on intensity, shape, size or volume, and texture offer information on tumor phenotype and microenvironment (or habitat) that is distinct from that provided by clinical reports, laboratory test results, and genomic or proteomic assays. These features, in conjunction with other (clinical) information, can be correlated with clinical outcomes data and used for evidence-based clinical decision support.

Furthermore, liquid biopsy analysis has become a new opportunity in translational cancer research and in clinical practice (58). Genetic profile of tumors is currently obtained from surgical or biopsy specimens, but biopsy represents a spatial and temporally limited snap-shot of a tumor. It has been shown that the initial surgical specimen might significantly differ from the molecular profile of its metastases (59). Moreover, the initial biopsy might not

reflect tumor heterogeneity and sequential biopsies can rarely be implemented in routine clinical care because of ethical, financial or logistical barriers. Liquid biopsies offer prognostic and predictive information, obtained by a minimally invasive, inexpensive and easily obtainable technique, where circulating tumor cells (CTC) and cell-free DNA (cfDNA) can be evaluated for the presence of genetic mutations/aberrations from a single blood sample.

Conclusions

In conclusion, it is important to understand the relationship between CT radiologic features of GGO and lung adenocarcinoma subtypes, according to the 2015 WHO classification standard. Furthermore, understanding the association of the presence of GGO, or GGO ratio, and molecular biomarkers, can guide targeted treatments, especially when a biopsy tissue or surgical specimen is not available.

In the near future we do expect that adjunctive tools will be able to help guiding the choice of treatment, will be radiomics and liquid biopsies.

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Footnote

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