Received:
22 February 2018

Revised:
13 September 2018

Accepted:
24 September 2018

<https://doi.org/10.1259/bjr.20180204>

Cite this article as:

Gao F, Sun Y, Zhang G, Zheng X, Li M, Hua Y. CT characterization of different pathological types of subcentimeter pulmonary ground-glass nodular lesions. *Br J Radiol* 2019; **91**: 20180204.

FULL PAPER

CT characterization of different pathological types of subcentimeter pulmonary ground-glass nodular lesions

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Objective To explore the CT characteristics of small lung nodules and improve the diagnosis of pulmonary ground-glass nodules less than 10 mm in size.

Methods We retrospectively analyzed CT images of 161 pulmonary nodules (less than 10 mm in size) with spiculation, lobulation, vacuoles, and pleural indentation and compared these images with pathological results or follow-up CT images. The relationships between the ground-glass nodules (GGNs) and blood vessels were observed. The GGN-vessel relationship was divided into four types, Type I (pass-by), Type II (pass-through), Type III (distorted/dilated), Type IV (complicated). The vessels traveling through a GGN were divided into three categories, category A (arteries), category B (veins), category C (arteries and veins).

Results 161 GGNs were divided into three groups (benign group, pre-invasive group, and adenocarcinoma group) according to their pathological diagnosis. Significant differences in density of nodules were observed among the three different groups ($p < 0.05$). Significant differences in the shape (round/round-like or not) of the nodules were observed between the benign group and the pre-invasive group and between the pre-invasive

group and the adenocarcinoma group ($p < 0.05$). No significant differences in the presence of vacuoles were observed between the benign group and the pre-invasive group or between the pre-invasive group and the adenocarcinoma group ($p > 0.05$), but a significant difference was observed between the benign group and the adenocarcinoma group ($p < 0.05$). The differences in the vascularization of the lesions among the three groups were statistically significant ($p < 0.05$). No significant differences or correlations were observed between vascular categories and GGN groups ($p > 0.05$).

Conclusion For subcentimeter nodules, mixed GGNs with vacuoles, well-defined border, combined with Type III or Type IV GGN-vessel relationship may strongly suggest malignant.

Advances in knowledge Previous studies mainly focused on CT diagnosis of pulmonary nodules (≤ 3 cm in diameter), but this study focused on ground-glass nodules less than 10 mm in diameter, which had not been fully studied. For subcentimeter nodules, mixed GGNs with vacuoles, well-defined border, especially the GGN-vessel relationship manifest as Type III (distorted/dilated) or Type IV (complicated) may strongly suggest malignant.

INTRODUCTION

In February 2011, a new lung adenocarcinoma classification was jointly announced by the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society. According to the new classification, the 5-year overall survival rate for patients with AIS (adenocarcinoma *in situ*) and MIA (minimally invasive adenocarcinoma) who receive surgery is approximately 100%.^{1–3} A definitive diagnosis of pulmonary small ground-glass nodules (GGNs) that are less than 10 mm in diameter is difficult to obtain using a CT scan,^{4,5} and aspiration biopsy usually does not generate a

definitive diagnosis due to the small size and low density of nodular lesions, which was emphasized in the new classification announcement. According to a statement about pulmonary nodule treatment from the Fleischner Society⁵ in 2017, GGNs < 6 mm in diameter do not require routine follow-up, but for GGNs ≥ 6 mm in diameter, the treatment strategies were set according to the diameter of solid component in the nodule. For persistent nodule and the solid component ≥ 6 mm in diameter, the nodule should be considered highly suspicious. We retrospectively analyzed CT images from 161 patients with small GGNs (less than 10 mm in diameter) who were diagnosed by pathology or

clinical follow-up in March 2011 through May 2014 to analyze the relationship between small GGNs and vessels and the value of CT in the differential diagnosis of small GGNs.

METHODS AND MATERIALS

Patients

Imaging data from patients with pulmonary GGNs who received a thin-section multidetector CT examination at our hospital in March 2011 through May 2014 were retrospectively reviewed. All lesions were GGNs (less than 10 mm in size), solitary, and most (152/161) were surgically resected within 2 weeks after CT scanning. 161 patients were enrolled in this study, including 54 males and 107 females with a mean age of 57.60 ± 11.41 years (range 22 to 81 years), and none of them had primary malignant tumor history.

All GGNs were divided into three groups according to their pathological diagnosis. 20 cases belonged to the benign group (9 cases disappeared in the subsequent CT scan after anti-inflammatory treatment or follow-up, and 11 cases were confirmed by surgery: 1 case of sclerosing hemangioma, 2 cases of hamartoma, and 8 cases of chronic inflammation). The pre-invasive group included 55 cases that were all diagnosed by surgery. The pre-invasive group comprised 17 cases of atypical adenomatous hyperplasia (AAH) and 38 cases of AIS (all of which were non-mucous lesions). 86 cases in the adenocarcinoma group were all diagnosed by surgery, including 56 cases of MIA and 30 cases of invasive adenocarcinoma (IAC) (all which were non-mucous lesions).

CT examination and image analysis

Chest CT imaging (ranging from the apex to the base of the lung, including the chest wall and axillary fossa) was performed with a 64-detector CT system (GE Light Speed VCT or GE Discovery CT750 HD, GE Healthcare, Milwaukee, WI) using the following scan parameters: 1.25 mm section width with a 1.25 mm reconstruction interval, pitch of 0.984, 120 kV, and automatic milliamp exposure (SmartmA; GE Healthcare, Waukesha, WI) technique was applied (range 40 ~ 400 mA, mean about 250mA), rotation time was 0.5 s. All images were reviewed with a high-resolution 52.8 cm, 2048 × 1560-pixel greyscale monitor with a standard lung window (window width, 1500 HU; window level, -500 HU) and mediastinal window (window width, 350 HU; window level, 50 HU).

In lung CT images, a GGN lesion is defined as a hazy increase in attenuation in the lung with preservation of intact bronchial and vascular structures.⁶⁻⁸ GGNs are further subdivided into mixed GGNs (mGGNs) and pure GGNs (pGGNs).⁹ The observer-recorded CT parameters include the following: 1) general CT features of GGNs, including the location, size (the average value of long and short axis axial diameter and craniocaudal height), and morphological features of nodules (round or not), presence of vacuoles, lobulation, spiculation, and pleura indentation; and 2) a blood vessel analysis (from the lesion to the hilum) to examine the vascular morphology, vascular affiliation (branches of pulmonary arteries or veins), and vascular relationships with GGN lesions using axial images, multiplanar reformation

images, and curved-planar reformatted images. Under normal conditions, the diameters of pulmonary vessels gradually decrease from the hilum toward the periphery. If the diameter of a vascular segment within a lesion is larger than the diameter of the proximal segment (before entering lesions) or if a lesion vessel is obviously wider than other vessels at the same branch level, the vessel is deemed as exhibiting abnormal vascular broadening. Vessels are considered distorted or rigid if they travel astray from the expected normal course. Multiple supplying vessels with different originating sources that converge toward a lesion are a probable indication of increased blood circulation within the lesion. We traced vascular courses through the slices backward to major vessels in the hilum to further clarify the affiliations of the supplying vessels. The relationships between the GGNs and the supplying blood vessels were categorized into four types according to the imaging features.⁹ Type I (pass-by): Vessels pass by GGNs without a detectable supply of branches to lesions (Figures 1-2). Type II (pass-through): Vessels pass through the lesions without obvious morphological changes in their path or size (Figures 1-2). Type III (distorted/dilated): Vessels located within lesions are tortuous or rigid, without an increase in the number of vessels (Figures 1-2). Type IV (complicated): Vessels display a more complicated vasculature in GGNs than described for the aforementioned types, such as the coexistence of irregular vascular dilation and vascular convergence from multiple supplying vessels (Figures 1-2).

Normal pulmonary vessels radiate from the hilum to periphery of the lung with tapering. Vessels are defined as thickening vessels if the tapering characteristics are lost or the distal vessels are broader than the proximal vessels or neighboring peer vessels (within the lesion or close to the lesion). We define a vessel as stiff or distorted when a vessel does not follow the normal course, and we define a vessel relationship as the extent to which aggregation increases if vessels converge toward the lesion combined with vessel stiffness (Figures 1-2, analysis of the relationship between GGNs and vessels). The imaging analysis was conducted by two experienced thoracic radiologists who were blinded to the pathological results. For every GGN case, each radiologist independently reported the lesion location, the GGN-vessel type, vascular affiliation (pulmonary artery or vein) and likelihood of malignancy or benignity. If a disagreement occurred, a consensus was reached after mutual discussion and/or consultation with a third senior radiologist.

Pathological diagnosis

AAH, AIS, MIA, and IAC were pathologically diagnosed and categorized based on the new pulmonary adenocarcinoma classification, 2011 edition.³ All histological preparations and analyses were performed by two senior pathologists. In the case of a disagreement, a consensus was reached after mutual discussion and/or consultation with a third pathologist.

Statistical analysis

Statistical analyses were performed with a commercially available computer software program (SPSS v. 16.0 for Windows, SPSS, Chicago, IL). An independent *t*-test was used to compare quantitative data. Correlations between pathological GGN findings and

Figure 1. (a–e) (a) Analysis of vessels in the images showing that the vessels are not correlated with the 5.5 mm nodule in the lower left lobe (arrow; Type I). (b) Analysis of vessels in the image showing a branch of the PV passing through the lesion without obvious morphological changes in its path or diameter (arrow; Type II). (c) Analysis of vessels in the image showing a broadened branch of the PA passing through the small nodule (arrow; Type III). (d–e) CPR image showing focal irregular dilation of a branch of the PV passing through the small nodule and no focal changes in the branch of the PA (arrow; Type IV). CPR, curved-planar reformatted; PV, pulmonary vein; PA, pulmonary artery.

GGN-vessel relationships were examined using the Spearman rank test, and conventional morphological features of nodules were compared among groups using Pearson's Chi-squared test.

Figure 2.(a–d) (a) VR image showing a branch of the PV that passed by the small GGN (arrow; Type I). (b) VR image showing a branch of the PV and a branch of the PA passing through the small nodule without morphological changes (Type II, category C). (c) VR image showing a broadened branch of the PA passing through the small nodule (Type III, category A). (d) VR image showing that the relationship of the nodule with the vessels is (arrow; Type IV, category C). GGN, ground-glass nodule; VR, volume-rendered.

When the expected value was <1 or the pre-test probability was approximately the same as the test level, Fisher's exact test was used instead. GGN-vessel relationships between patients with MIA and IAC were compared using Pearson's Chi-squared test. When the expected value was <1 or the pre-test probability was similar to the test level, Fisher's exact test was used instead. Statistical results were considered significant when the p value was less than 0.05.

RESULTS

GGN sizes and density

The mean sizes of GGNs in the benign, pre-invasive, and adenocarcinoma groups were 6.90 ± 1.36 mm, 6.22 ± 1.48 mm, and 7.55 ± 1.41 mm, respectively. No statistically significant differences in the size of GGNs were observed between the benign group and the pre-invasive group or between the benign group and the adenocarcinoma group ($t = 1.860$, $p = 0.071$; $t = -1.912$, $p = 0.066$, respectively). A statistically significant difference was observed between the pre-invasive group and the adenocarcinoma group ($t = -5.290$, $p = 0.000$), indicating that the GGNs

Table 1. Comparison among groups of conventional morphological features

	Benign group (20 cases)	Pre-invasive group (55 cases)	Adenocarcinoma group (86 cases)	Benign vs pre-invasive (<i>p</i> value)	Pre-invasive vs adenocarcinoma (<i>p</i> value)	Benign vs adenocarcinoma (<i>p</i> value)
Density (mGGN) ^a	6	4	53	0.010	0.010	0.000
Round/round-like	12	49	57	0.004	0.002	0.596
Spiculation	3	6	17	0.630	0.165	0.624
Lobulation	6	12	31	0.463	0.073	0.609
Vacuole	0	6	15	0.124	0.288	0.044
Well-defined border	12	53	77	0.000	0.140	0.001
Pleural indentation	4	12	23	0.865	0.533	0.509

GGN, ground-glass nodule;

^amGGN, GGN with mixed density.

of the adenocarcinoma group were bigger than the GGNs of the pre-invasive group.

Significant differences in density of nodules were observed among the three different groups ($p < 0.05$) (Table 1); when the nodule shows mixed density it is more likely to be malignant.

Morphological features observed with conventional CT

Statistically significant differences in the shape (round/round-like or not) of nodules were observed between the benign group and the pre-invasive group and between the pre-invasive group and the adenocarcinoma group ($p < 0.05$), but no statistically significant differences were observed between the benign group and the adenocarcinoma group ($p > 0.05$). Pre-invasive nodules displayed a round shape (49/55) to a greater extent than benign (12/20) and adenocarcinoma (57/86) nodules (Table 1).

Significant differences in the border (well-defined or not) of nodule were observed between the benign group and the pre-invasive group and between the benign group and the adenocarcinoma group ($p < 0.05$) but not between the pre-invasive group and the adenocarcinoma group ($p > 0.05$). Compared to the benign group, nodules in the pre-invasive group and adenocarcinoma group were more likely to show well-defined border.

No statistically significant differences in the presence of vacuoles were observed between the benign group and the pre-invasive

group or between the pre-invasive group and the adenocarcinoma group ($p > 0.05$), but a statistically significant difference was observed between the benign group and the adenocarcinoma group ($p < 0.05$).

No significant differences in spiculation, lobulation, or pleural indentation were observed among the three different groups ($p > 0.05$, Table 1).

Multidetector CT examination of the relationship between GGN and vessels

GGN-vessel relationships were categorized into four types according to their imaging features: Type I pass-by, 21 cases (Figures 1–2); Type II pass-through, 80 cases (Figures 1–2); Type III distorted/dilated, 35 cases (Figures 1–2); Type IV complicated, 25 cases (Figures 1–2).

In this study, 85% (17/20) of cases in the benign group, 74.44% (41/55) of cases in the pre-invasive group, and 95.34% (82/86) of cases in the adenocarcinoma group displayed vessels that passed through the lesion (total numbers of Types II, III, and IV). The differences in vessels passing through lesions among the three groups were statistically significant ($\chi^2 = 13.6526$, $p = 0.001$). The number of cases with Type I, II, III, and IV GGN-vessel relationships were significantly different among the three groups ($p < 0.05$; Table 2). The most common GGN-vessel relationships were Type II for the benign group and Types I and II for the pre-invasive group. A few GGNs in the benign and pre-invasive

Table 2. Different pathological GGNs and vessel relationship types (161 cases)

GGN-vessels relationships	Type I (21 cases)	Type II (80 cases)	Type III (35 cases)	Type IV (25 cases)
Benign group (20 cases)	3 (15.00%)	14 (70.00%)	2 (10.00%)	1 (5.00%)
Pre-invasive group (55 cases)	14 (25.45%)	34 (61.82%)	5 (9.09%)	2 (3.64%)
Adenocarcinoma group (86 cases)	4 (4.65%)	32 (37.21%)	28 (32.56%)	22 (25.58%)
χ^2	12.877	11.895	12.709	14.246
p^a	0.002	0.003	0.002	0.001

GGN, ground-glass nodule;

Type I (pass-by), Type II (pass-through), Type III (distorted/dilated), Type IV (complicated).

^aThe p -value refers to the diagnostic value of different type of GGNs-vessel relationship among the three groups.

groups manifested as Types III and IV GGN-vessel relationships. In the adenocarcinoma group, most GGNs manifested as Type II, III, and IV relationships (Table 2). According to the pathological results, the pre-invasive group was divided into the AAH sub group and the AIS sub group. 7, 10, 0, and 0 cases in the AAH sub group and 7, 24, 5, and 2 cases in the AIS sub group displayed Types I, II, III, and IV GGN-vessel relationships, respectively. The differences in the GGN-vessel relationships among these two sub groups were not statistically significant ($\chi^2 = 5.557$, $p = 0.135$). According to the pathological results, the adenocarcinoma group was divided into an MIA sub group and an IAC sub group. 4, 24, 20, and 8 cases in the MIA sub group and 0, 8, 8, and 14 cases in the IAC sub group exhibited Type I, II, III, and IV GGN-vessel relationships, respectively. The differences in GGN-vessel relationships between these two sub groups were statistically significant ($\chi^2 = 12.017$, $p = 0.007$). The pathological etiology of GGNs was significantly correlated with the GGN-vessel relationships (analysis of three groups: benign, pre-invasive, and adenocarcinoma groups, $r = 0.447$, $p = 0.000$; analysis of five sub groups: benign, AAH, AIS, MIA, and IAC sub groups, $r = 0.511$, $p = 0.000$).

Correlations between GGN groups and pulmonary veins/arteries

The vessels traveling through a GGN were arteries (category A), veins (category B), or arteries and veins (category C). No significant differences or correlations were observed between vascular categories and GGN groups ($p > 0.05$). Therefore, the vascular category had little value in the differential diagnosis of GGNs based on the correlation analysis between GGN groups and pulmonary veins/arteries (Table 3). The pathological etiology of GGNs was not significantly associated with GGN-vessel relationships ($p = 0.292$).

DISCUSSION

Based on clinical data, nodule size is an independent predictive factor for malignancy, as increases in the GGN size increase the likelihood of malignancy.¹⁰ Our research focuses on GGNs less than 10 mm in diameter, which was very small, and our result shows that nodules in the pre-invasive group were smaller than GGNs in the adenocarcinoma group, which was in accordance with previous study.¹¹ And our result also shows that when the nodule shows mixed density it is more likely to be malignant; this is also consistent with Yoon et al's study.¹²

Based on the results of this study, statistically significant differences in the shape (round/round-like or not) of nodules were observed between the benign group and the pre-invasive group and between the pre-invasive group and the adenocarcinoma group ($p < 0.05$), but not between the benign group and the adenocarcinoma group ($p > 0.05$). Pre-invasive lesions more frequently displayed a round or round-like morphology, and benign lesions and adenocarcinomas more frequently displayed irregular shapes. Lesions with a predominantly lepidic growth pattern include pre-invasive lesions and MIA, and invasive adenocarcinomas with a predominantly lepidic growth pattern more frequently display a round or round-like morphology than other types of lung adenocarcinomas.¹³ These patterns correspond to the pathological correlations of these lesions. When lesions exhibit a predominantly lepidic growth pattern, they have a small or no invasive component (they do not invade surrounding tissues or exhibit alveolar collapse). In these situations, the lesions display a round or round-like morphology. The morphology of the lesions becomes increasingly irregular as the lesions display a predominantly invasive growth pattern. The irregular morphology is caused by differences in the differentiation and growth velocities between tumor cells in different regions of the tumor and contraction caused by intratumor fibrosis.

The result of this study shows that no significant differences in spiculation, lobulation, or pleural indentation were observed among the three different groups. This may be because the nodules in our study were very small, and most CT morphological features of lung cancer could not be clearly presented. According to the study by Wu et al,¹⁴ vessel changes, an irregular margin, and a clear lung-tumor interface may indicate the invasiveness of lung adenocarcinoma with subcentimeter pGGNs. Our results show the increased frequency of vacuoles and a well-defined border in adenocarcinomas compared with benign lesions; this was similar to the conclusions reported by Wu et al. However, in this study there was no statistically significant differences between benign group and adenocarcinoma group in some conventional morphological features (such as shape of nodule, spiculation, lobulation, and pleural indentation). Based on clinical experience, some common CT features of malignant nodules, such as pleural indentation, spiculation, and lobulation, are rarely observed in very early stage malignant GGNs, and this also make the diagnosis and differential diagnosis of small GGNs

Table 3. The correlation between GGN groups and pulmonary veins/arteries (140 cases)

Group	Category A (41 cases)	Category B (59 cases)	Category C (40 cases)
Benign group (17 cases)	8 (47.06%)	5 (29.41%)	4 (23.53%)
Pre-invasive group (41 cases)	13 (31.71%)	14 (34.15%)	14 (34.15%)
Adenocarcinoma group (82 cases)	20 (24.39%)	40 (48.78%)	22 (26.83%)
χ^2	3.658	3.687	0.958
p^a	0.161	0.158	0.619

GGN, ground-glass nodule ;

Category A, only arteries traveling through the GGN; Category B, only veins traveling through the GGN; Category C: both arteries and veins traveling through the GGN.

^aThe p -value refers to the diagnostic value of different category of vessel among the three groups

very difficult.^{15–17} The densities of these lesions were also very low and similar to lung tissue; this low density may exacerbate the difficulties in analyzing the morphological features. So when it comes to subcentimeter GGNs, it may be difficult to obtain those typical morphological features that were used to diagnose solid nodules in the lung, such as pleural indentation, spiculation, and lobulation.¹⁸ However, our study shows that the presence of vacuoles in the nodule or a well-defined border may help in the differential diagnosis of benign lesions and adenocarcinomas, consistent with the results reported by Wu et al.¹⁴ And the study by Nambu et al¹⁶ also suggest that vacuoles are a very important sign of malignant lesions.

In our previous study, we divided the GGN-vessel relationships into four types,¹⁹ and in this study, we also divided the GGN-vessel relationships of subcentimeter GGNs into four types. GGN-vessel relationships significantly differed among the three groups of GGNs. Concurrently, a statistically significant difference was observed between the MIA sub group and IAC sub group of the adenocarcinoma group ($p = 0.040$), and the pathological etiology of GGNs was significantly associated with the GGN-vessel relationships.

Combined with Noguchi's hypothesis^{20–22} regarding mechanisms that generate vascular convergence signs, the fibrosis reaction was the main mechanism that generated Type III and Type IV GGN-vessel relationships. Central fibrosis and subsequent tissue contraction have been reported to generate fibrotic strands around the tumor, and the fibrotic foci become larger as the invasive grade of the tumor increases; this fibrosis also causes vessel contraction.¹⁵ In addition, malignant lesions exhibit greater growth and metabolism than normal tissue and thus require more blood flow. The increased growth and metabolism may induce the surrounding vessels to broaden.

In our study, one case in the benign group displayed a Type IV GGN-vessel relationship, and two cases displayed as Type III GGN-vessel relationships. Fibrosing hyperplasia can be seen in

benign GGNs less than 10 mm, and inflammatory hyperemia also may cause Type III and Type IV GGN-vessel relationships. However, these morphological changes are rarely observed in benign lesions compared with malignant lesions. If Type III or Type IV GGN-vessel relationships were observed, then the vessels pass through the GGNs with or without vascular convergence from multiple supplying vessels or are tortuous or rigid without an increase in number combined with the broadening of the vessel diameter. GGNs should be highly suspected as lung adenocarcinomas when Type III or Type IV GGN-vessel relationships are observed. However, vascular affiliation analysis has little value for the differential diagnosis of GGNs.

The major limitation of this study was that, as a retrospective analysis, the patients in this study almost all had pathology, so the lesion may be more larger and with more suspicious features; this may lead to bias in the results, and since the number of samples in our study is relatively small, particularly in the benign group, further studies are required in the future. In this study we only simply classified the GGNs into pGGNs and mGGNs according to their density, but the solid component in the nodule had not been measured and analyzed, and we will add this in the future study.

In conclusion, although the diagnosis of GGNs less than 10 mm is very difficult, a comprehensive analysis of morphological features in CT images, such as mixed density, the presence of vacuoles, and a well-defined border, combined with Type III and Type IV GGN-vessel relationships may effectively suggest a malignant etiology of GGNs. In the clinical practice if subcentimeter GGNs appear with those morphological features, then it may need to shorten the interval of the follow-up or further examinations, but this still needs future study.

FUNDING

This study was supported by the Research Programme of Shanghai Hospital Development Center (SHDC22015025); the Medical Imaging Key Program of Wise Healthcare Technology 120, Health Commission of Shanghai (2018ZHYL0103).

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