Thoracic Cancer
Open Access
Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

Clinical characteristics of resected solitary ground-glass opacities: Comparison between benign and malignant nodules

Yingzhi Qin†, Yuan Xu†, Dongjie Ma, Zhenhuan Tian, Cheng Huang, Xiaoyun Zhou, Jia He, Lei Liu, Chao Guo, Guige Wang, Jiaqi Zhang, Yanqing Wang & Hongsheng Liu

Department of Thoracic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, China

Keywords
Benign; ground-glass opacity; malignant; surgery.

Correspondence
Hongsheng Liu, Department of Thoracic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Dongcheng District, Beijing, China.
Tel: +86 15120003100
Fax: +86-010-69152630
Email: mdzyxy@gmail.com

†Yingzhi Qin and Yuan Xu are co-first authors.

Received: 14 May 2020;
Accepted: 21 June 2020.

doi: 10.1111/1759-7714.13575

Thoracic Cancer **11** (2020) 2767–2774

Abstract

Background: The management of ground-glass opacities (GGOs) depends mainly on personal experience. In clinical practice, benign GGOs are not rare in resected specimens, for which operations may be avoided. We retrospectively compared the clinical features of resected GGOs to identify differential diagnostic characteristics.

Methods: Among 1456 patients with suspected malignant GGOs who underwent surgical resection, 105 patients (35 with benign GGOs and 70 matched controls with malignant GGOs) were included. Clinical characteristics, including demographics and radiologic, surgical and pathologic characteristics, were collected.

Results: The smoking index (P = 0.044), frequency of coughing (P = 0.026), GGO size (P = 0.003), size change during follow-up (P = 0.011), location (P = 0.022), presence of air bronchogram sign (P = 0.004), distance to the pleura (P = 0.021) and positron emission tomography/computed tomography (PET/CT) appearance (P = 0.003) showed significant differences between the benign and malignant groups. Pathologically, the resected benign GGOs included focal fibrosis (17), inflammation or infection (seven), lymphoproliferative disorder (one), hamartoma (three), inflammatory myofibroblastic tumor (two), hemangioma or vascular malformation (two), endometriosis (two) and pulmonary cyst (one).

Conclusions: A higher smoking index, coughing, larger size, similar or increased size during follow-up, location in the upper and middle lobes, air bronchogram sign on CT, lesion margin to pleura distance over 1 cm, and malignant tendency on PET/CT reports were associated with malignant GGOs. Relatively active surgical interventions could be considered for GGOs highly suspected of malignancy.

Introduction

Ground-glass opacities (GGOs) on computed tomography (CT) are defined as hazy opacities with preserved bronchial and vascular margins in the lung parenchyma.[1] With the availability of low-dose spiral CT scans of the lung, the detection of GGOs has increased rapidly. Pathologically, GGOs may be caused by partial airspace filling, interstitial thickening with inflammation, edema, fibrosis, neoplastic proliferation, normal respiratory conditions or increased pulmonary capillary blood volume.[2]

Although GGOs are nonspecific CT findings, the management of GGOs has gained increasing attention as these nodules may indicate lung cancer, most of which are adenocarcinomas. Several guidelines on GGO management have been published. In clinical practice, nonetheless, the decision to offer surgery and the timing of surgery still

 © 2020 The Authors. *Thoracic Cancer* published by China Lung Oncology Group and John Wiley & Sons Australia, Ltd
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

highly depend on personal experience. How to distinguish between benign and malignant GGOs remains a problem. Many studies have highlighted the radiologic characteristics of GGOs. However, well-recognized features of malignant GGOs are scarce. We herein report the clinical characteristics of resected GGOs, which were highly suspected to be malignant before surgery. The aim of this study was to retrospectively compare the clinical characteristics of benign and malignant GGOs in an attempt to identify characteristics that would assist in the differential diagnosis of these nodules and to help the future determination of resection necessity. A discussion of surgical strategy based on our experience is provided.

Methods

Patients

Between January 2016 and December 2019, 1456 patients at Peking Union Medical College Hospital in Beijing, China, were suspected to have malignant GGOs based on outpatient evaluations and underwent surgical resection. Of these patients, we excluded those with the following: (i) more than one nodule (n = 764); (ii) pathologically malignant nodules (n = 646, including atypical adenomatous hyperplasia); and (iii) unavailable entire pathologic sections (n = 7) or no lesion after resection (n = 4). Ultimately, 35 patients were included in this study (Fig 1).

Patients with benign GGOs were matched at a ratio of 1:2 with controls based on sex and age (± five years). The matched controls included only patients with histologically confirmed malignant GGOs and were identified from our prospective database during the same period as the benign cases. The case control matching function of SPSS was used to conduct this randomized matching.

Clinical evaluation

All clinical features, including demographic information (age, sex), personal history (smoking history, drinking history, malignant tumor history, family history of lung cancer in a first-degree relative), and clinical features (manifestation, comorbidity, history of anti-inflammatory therapy and follow-up time), were retrospectively collected from the medical records and our prospective database. Descriptions of the variables are listed in Table S1.

Radiologic evaluation

All GGOs were evaluated using high-resolution CT (slice thickness = 2.5 mm) images within one month before surgery. The CT characteristics, including tumor size, spicule sign, vessel convergence sign, lobulated sign, calcifications, pleural indentation, thick wall cavity, thin wall cavity, air bronchogram sign, and vacuole sign, were reviewed blindly by two experienced thoracic surgeons. Any discrepancies were resolved by discussion with the third surgeon. The definitions of the characteristics are listed in Table S1.

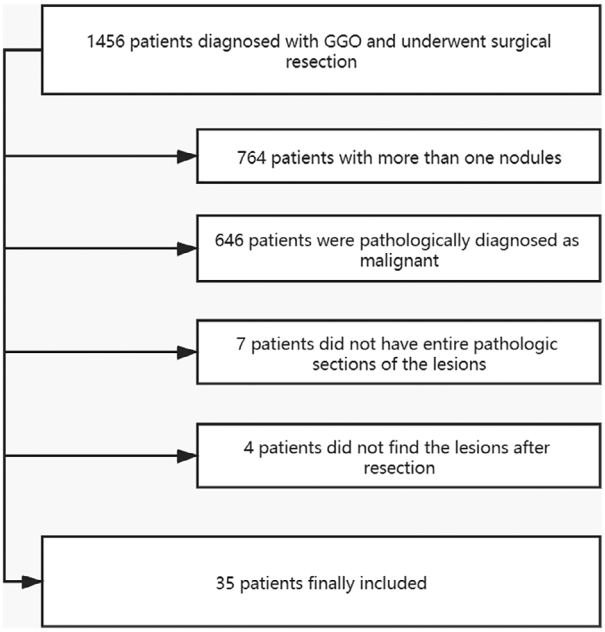

Figure 1 Flow chart of patient enrollment.

Positron emission tomography/computed tomography (PET/CT) was performed for systemic evaluation within one month before surgery. The PET/CT images were evaluated by nuclear medicine physicians (>12 years of experience in PET/CT interpretation) before surgery. Notably, some patients chose other auxiliary examinations (i.e., MRI, CT or B-mode ultrasound) for systemic evaluation, as PET/CT is expensive and not usually covered by medical insurance.

Surgical management and pathological examination

The strict indications for surgical interventions included: (i) a pure GGO with diameter 8–15 mm becoming larger or where a solid component or other malignant signs appeared during follow-up; (ii) a pure persistent GGO with a diameter >15 mm, or becoming larger after a 3–6-month follow-up period; and (iii) a mixed persistent GGO, or becoming larger after a 3-month follow-up period. The relative indications for GGOs with diameters of 5–8 mm included: (i) a GGO located close to the pleura and suitable for wedge resection; (ii) a GGO highly resembling malignancy upon CT scan (i.e., containing a solid component, lobulated sign, pleural indentation or spicule sign); and

 © 2020 The Authors. *Thoracic Cancer* published by China Lung Oncology Group and John Wiley & Sons Australia, Ltd

(iii) the patient being extremely anxious and unable to tolerate follow-up. All patients underwent video-assisted thoracoscopic surgery (VATS). The GGOs were completely resected via wedge resection, segmentectomy or lobectomy of the lung. The surgical information (description of pleural adhesions and hydrothorax) was recorded by the surgeon. When necessary, an intraoperative frozen section (FS) was made during surgery. All resected GGOs were examined by routine pathology. The specimens were examined by experienced pathology specialists, whose observations were recorded. The pathological diagnoses were based on the 2015 World Health Organization criteria.[3, 4]

Statistical analysis

Comparisons were made using the independent-samples *t*-test, the two-sample Kolmogorov–Smirnov test, the chi-square test or the Mann-Whitney U test, as appropriate. The Shapiro-Wilk test was used to evaluate if the variables followed a normal distribution (Table S2). A two-sided $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS 22.0 software (IBM Corp., Armonk, NY, USA).

Results

A total of 105 patients with solitary pulmonary GGOs were retrospectively analyzed. The comparison of clinical characteristics between the benign and malignant groups is shown in Table 1. The average patient age was 53.9 years, and 31.4% were males. A total of 16 (22.6%) patients had a history of smoking, with no between-group difference (17.1% vs. 14.3%, $P = 0.701$). However, smokers in the malignant group showed a higher smoking index than those in the benign group ($P = 0.044$). The incidence of cough was significantly different between the benign and malignant groups (2.9% vs. 18.6%, $P = 0.026$), with no differences observed in hemoptysis (2.9% vs. 1.4%, $P = 0.614$), abnormal phlegm (2.9% vs. 8.6%, $P = 0.268$) or fever (8.6% vs. 7.1%, $P = 0.795$). A history of anti-inflammatory therapy was present in 34.3% and 28.6% of the benign and malignant groups, respectively ($P = 0.549$). The median follow-up time seemed longer in the benign group (120 days) than in the malignant group (90 days), although the difference was not significant. Notably, GGOs were more common to get larger in the benign group than in the malignant group (34.3% vs. 21.4%). The GGOs in three patients decreased in size, and all were benign. There

Table 1 Comparison of the clinical characteristics of patients with solitary pulmonary GGOs

Variable	Overall (*n* = 105)	Benign (*n* = 35)	Malignant (*n* = 70)	*P*-value
Demographic information				
Age (± SD) (years)	53.9 (±12.4)	53.9 (±12.5)	53.9 (±12.4)	0.983
Sex, n (%)				
Male	33 (31.4%)	11 (31.4%)	22 (31.4%)	1.000
Female	72 (68.6%)	24 (68.6%)	48 (68.6%)	
Smoking history, n (%)	16 (15.2%)	6 (17.1%)	10 (14.3%)	0.701
Smoking index (median, [IQR])				
Overall	0 (0)	0 (0)	0 (0)	0.858
Smokers only	425 (556)	300 (447)	700 (900)	**0.044**
Drinking history, n (%)	11 (10.5%)	4 (11.4%)	7 (10.0%)	0.822
History of malignant tumor, n (%)	4 (3.8%)	2 (5.7%)	2 (2.9%)	0.471
Family history of lung cancer, n (%)	8 (7.6%)	1 (2.9%)	7 (10.0%)	0.193
Clinical information				
Manifestation, n (%)				
Cough	14 (13.3%)	1 (2.9%)	13 (18.6%)	**0.026**
Hemoptysis	2 (1.9%)	1 (2.9%)	1 (1.4%)	0.614
Abnormal phlegm	7 (6.7%)	1 (2.9%)	6 (8.6%)	0.268
Fever	8 (7.6%)	3 (8.6%)	5 (7.1%)	0.795
Comorbidity, n (%)				
Hypertension	30 (28.6%)	7 (20.0%)	23 (32.9%)	0.169
Diabetes	5 (4.8%)	1 (2.9%)	4 (3.3%)	0.517
Impaired liver function	23 (21.9%)	4 (11.4%)	19 (27.1%)	0.066
Impaired kidney function	29 (27.6%)	12 (34.3%)	17 (24.3%)	0.280
Ventilation dysfunction	8 (7.6%)	5 (14.3%)	3 (4.3%)	0.069
Weight loss (median, [IQR]) (kg)	0 (0)	0 (0)	0 (0)	0.461
History of anti-inflammatory therapy, n (%)	32 (30.5%)	12 (34.3%)	20 (28.6%)	0.549
Follow-up time (median, [IQR]) (days)	120 (210)	120 (305)	90 (173)	0.165

Descriptions of the variables are listed in Table S1. IQR, interquartile range; SD, standard deviation.

 © 2020 The Authors. *Thoracic Cancer* published by China Lung Oncology Group and John Wiley & Sons Australia, Ltd

Table 2 Comparison of the radiologic findings of GGOs

Variable	Overall (*n* = 105)	Benign (*n* = 35)	Malignant (*n* = 70)	*P*-value
GGO feature, n (%)				
Pure GGO	30 (28.6%)	8 (22.9%)	22 (31.4%)	0.261
GGO-predominant	41 (39%)	12 (34.3%)	29 (41.4%)	
Solid-predominant	34 (32.4%)	15 (42.9%)	19 (27.1%)	
Involved lobes, n (%)				
Upper + middle	75 (71.4%)	20 (57.1%)	55 (78.6%)	**0.022**
Lower	30 (28.6%)	15 (42.9%)	15 (21.4%)	
Tumor size (median, (IQR)) (cm)	1.1 (0.9)	1.0 (0.4)	1.2 (0.9)	**0.003**
Size change during follow-up, n (%)				
No change	75 (71.4%)	20 (57.1%)	55 (78.6%)	**0.011***
Larger	27 (25.7%)	12 (34.3%)	15 (21.4%)	
Smaller	3 (2.9%)	3 (8.6%)	0 (0%)	
CT characteristics				
Spicule sign, n (%)	66 (62.9%)	20 (57.1%)	46 (65.7%)	0.392
Vessel convergence sign, n (%)	58 (55.2%)	19 (54.3%)	39 (55.7%)	0.890
Lobulated sign, n (%)	68 (64.8%)	20 (57.1%)	48 (68.6%)	0.248
Calcifications, n (%)	1 (1%)	1 (2.9%)	0 (0%)	0.155
Pleural indentation, n (%)	38 (36.2%)	9 (25.7%)	29 (41.4%)	0.114
Thick wall cavity, n (%)	5 (4.8%)	2 (5.7%)	3 (4.3%)	0.746
Thin wall cavity, n (%)	2 (1.9%)	1 (2.9%)	1 (1.4%)	0.614
Air bronchogram sign, n (%)	31 (29.5%)	4 (11.4%)	27 (38.6%)	**0.004**
Vacuole sign, n (%)	52 (49.5%)	17 (48.6%)	35 (50.0%)	0.890
Distance to pleural <1 cm, n (%)	68 (64.8%)	28 (80.0%)	40 (57.1%)	**0.021**
PET/CT diagnosis*, n (%)				
Benign	11 (15.5%)	8 (32.0%)	3 (6.5%)	**0.018**
Malignant	40 (56.3%)	11 (44.0%)	29 (63.0%)	
Uncertain	20 (28.2%)	6 (24.0%)	14 (30.4%)	
SUVmax* (median, [IQR])	0.9 (1.2)	0.9 (0.8)	0.8 (1.2)	0.870

Descriptions of the variables are listed in Table S1. CT, computed tomography; IQR, interquartile range; PET, positron emission tomography; SUV, standardized uptake value.

**P* is 0.087 when comparing the no-change group and the larger group.

were no significant differences regarding drinking history (11.4% vs. 10.0%, $P = 0.822$), history of malignant tumors (5.7% vs. 2.9%, $P = 0.471$), family history of lung cancer (2.9% vs. 10.0%, $P = 0.193$), hypertension (20.0% vs. 32.9%, $P = 0.169$), diabetes (2.9% vs. 3.3%, $P = 0.517$), impaired liver function (11.4% vs. 27.1%, $P = 0.066$), impaired kidney function (34.3% vs. 24.3%, $P = 0.280$) or ventilation dysfunction (14.3% vs. 4.3%, $P = 0.069$).

The radiologic findings of the GGOs are shown in Table 2. There were no differences in the distribution of pure GGOs (22.9% vs. 31.4%), GGO-predominant nodules (34.3% vs. 41.4%) and solid-predominant nodules (42.9% vs. 27.1%) between the benign and malignant groups ($P = 0.261$). The details of the involved lobes are listed in Table S3. In both groups, nodules in the upper and middle lobes appeared more frequently involved than those in the lower lobes. Significantly more GGOs were present in the lower lobes in the benign group than in the malignant group (42.9% vs. 21.4%, $P = 0.022$). The median nodule size was smaller in the benign group (1.0 vs. 1.2, $P = 0.003$). The benign group showed fewer air bronchogram signs (11.4% vs. 38.6%, $P = 0.004$). More GGOs were located less than 1 cm from the pleura in the benign group (80.0% vs. 57.1%), $P = 0.021$). Other characteristics, that is, spicule sign (57.1% vs. 65.7%, $P = 0.392$), vessel convergence sign (54.3% vs. 55.7%, $P = 0.890$), lobulated sign (57.1% vs. 68.6%, $P = 0.248$), calcifications (2.9% vs. 0%, $P = 0.155$), pleural indentation (25.7% vs. 41.4%, $P = 0.114$), thick wall cavity (5.7% vs. 4.3%, $P = 0.746$), thin wall cavity (2.9% vs. 1.4%, $P = 0.614$), and vacuole sign (48.6% vs. 50.0%, $P = 0.890$), showed no between-group differences.

PET/CT was conducted in 71 patients. After excluding uncertain diagnoses, the sensitivity of PET/CT for malignant GGOs was 90.6% (=29/[29 + 3]), and the specificity was 42.1% (=8/[8 + 11]). The positive predictive value was 72.5% (=29/[29 + 11]), and the negative predictive value was 72.7% (=8/[8 + 3]). The maximum standardized uptake (SUVmax) values were similar between the benign and malignant groups (0.9 vs. 0.8, $P = 0.870$).

Tables 3 and 4 summarize the pathological patterns of the benign and malignant GGOs, respectively. For benign

 © 2020 The Authors. *Thoracic Cancer* published by China Lung Oncology Group and John Wiley & Sons Australia, Ltd

Table 3 Pathological patterns of the benign GGOs

Type	N (n%)
Focal fibrosis	17 (48.5%)
Inflammation or infection	
Granuloma	3 (8.5%)
Tuberculosis	1 (2.9%)
Aspergillus	1 (2.9%)
Others	2 (5.7%)
Lymphoproliferative disorder	1 (2.9%)
Hamartoma	3 (8.5%)
Inflammatory myofibroblastic tumor	2 (5.7%)
Hemangioma or vascular malformation	2 (5.7%)
Endometriosis	2 (5.7%)
Pulmonary cyst	1 (2.9%)

Table 4 Pathological findings of the malignant GGOs

Variable	N (n%)
Adenocarcinoma subtypes	
AIS	10 (14.3%)
MIA	7 (10.0%)
IA	
Lepidic predominant	30 (42.9%)
Acinar predominant	20 (28.6%)
Papillary predominant	3 (4.3%)
Pathologic stage	
0	4 (5.7%)
IA1	25 (35.7%)
IA2	27 (38.6%)
IA3	7 (10.0%)
IB	5 (7.1%)
IIB	2 (2.9%)

Subtypes of adenocarcinoma are based on the 2015 WHO classification of lung tumors.

GGOs, the most common was focal fibrosis (48.7%). Four GGOs (20.0%), including three granulomas, one tuberculosis infection and one aspergillus infection, showed inflammation. The other pathological types included lymphoproliferative disorder (one, 2.9%), hamartoma (three, 8.5%), inflammatory myofibroblastic tumor (two, 5.7%), hemangioma or vascular malformation (two, 5.7%), endometriosis (two, 5.7%) and pulmonary cyst (one, 2.9%). High-resolution CT (HRCT) images of each benign disease are shown in Fig 2. With regard to malignant GGOs, the numbers of adenocarcinomas in situ (AIS), microinvasive adenocarcinomas (MIAs) and invasive adenocarcinomas (IAs) were 10 (14.3%), seven (10.0%), and 53 (75.7%), respectively. Lepidic predominant adenocarcinoma (LPA) accounted for the largest proportion (30, 42.9%). Most of the malignant GGOs were stage IA (59, 84.3%). The accuracy of FS pathology was similar between the benign and malignant groups (93.9% vs. 86.6%, $P = 0.268$) (Table S4).

Discussion

In the present study, we reported 35 patients with benign GGOs through a retrospective analysis of 1456 resected GGOs. We summarized the clinical features, imaging manifestations and pathological features of benign GGOs and compared benign and matched malignant cases. This case series, to the best of our knowledge, is the first to evaluate the clinical characteristics of resected benign GGOs.

Previous studies have found that GGOs do not necessarily indicate malignancy.[5–7] Benign conditions, including focal interstitial fibrosis,[5] infection, inflammatory processes or pulmonary hemorrhage,[8] can present as GGOs on CT. Our present study provided pathological patterns of resected benign solitary GGOs. Focal fibrosis was identified in 17 cases (48.5%) and infection/inflammation in seven cases (20.0%). In addition, we reported cases of lymphoproliferative disorder, hamartoma, inflammatory myofibroblastic tumor, hemangioma or vascular malformation, endometriosis and pulmonary cyst, some of which have not been previously reported. The main components of focal fibrosis are interstitial septal thickening with fibroblast proliferation and preservation of the intra-alveolar airspace, and the solid components may be related to the presence of fibrotic foci or alveolar collapse.[7] Some of the pathologic changes are irreversible, which may explain why GGOs do not disappear during follow-up. Inflammation can be related to any kind of infectious pneumonia, but cytomegalovirus (CMV) and *Pneumocystis jirovecii* are the most frequently reported.[9] Several reports of pulmonary hemorrhage presenting as a GGO have been reported in the literature,[10, 11] but this was not observed in our study. Patients with pulmonary hemorrhage should have been identified during outpatient evaluations; thus, no surgery was performed.

The differential diagnoses between benign and malignant GGOs are based mainly on personal experience. Several studies have investigated the risk factors of malignancy. GGO size is a well-recognized indicator.[12] We also observed a correlation between GGO size and malignancy. Previous studies also suggested that an increase in size or solid component might predict a malignant tendency.[13, 14] In our study, we did not observe a significant increase in size ($P = 0.087$). This might be because the follow-up time in our study was shorter than that in other studies, which were usually long-term studies.

Sawada *et al.* suggested that a higher consolidation diameter/tumor diameter (C/T) ratio was associated with invasive cancer.[13] Our study shows that the C/T ratio was not a risk factor for malignant GGOs, as there were no between-group differences in the distribution of pure GGOs, GGO-predominant nodules and solid-predominant nodules. Air bronchogram signs were another CT feature

 © 2020 The Authors. *Thoracic Cancer* published by China Lung Oncology Group and John Wiley & Sons Australia, Ltd

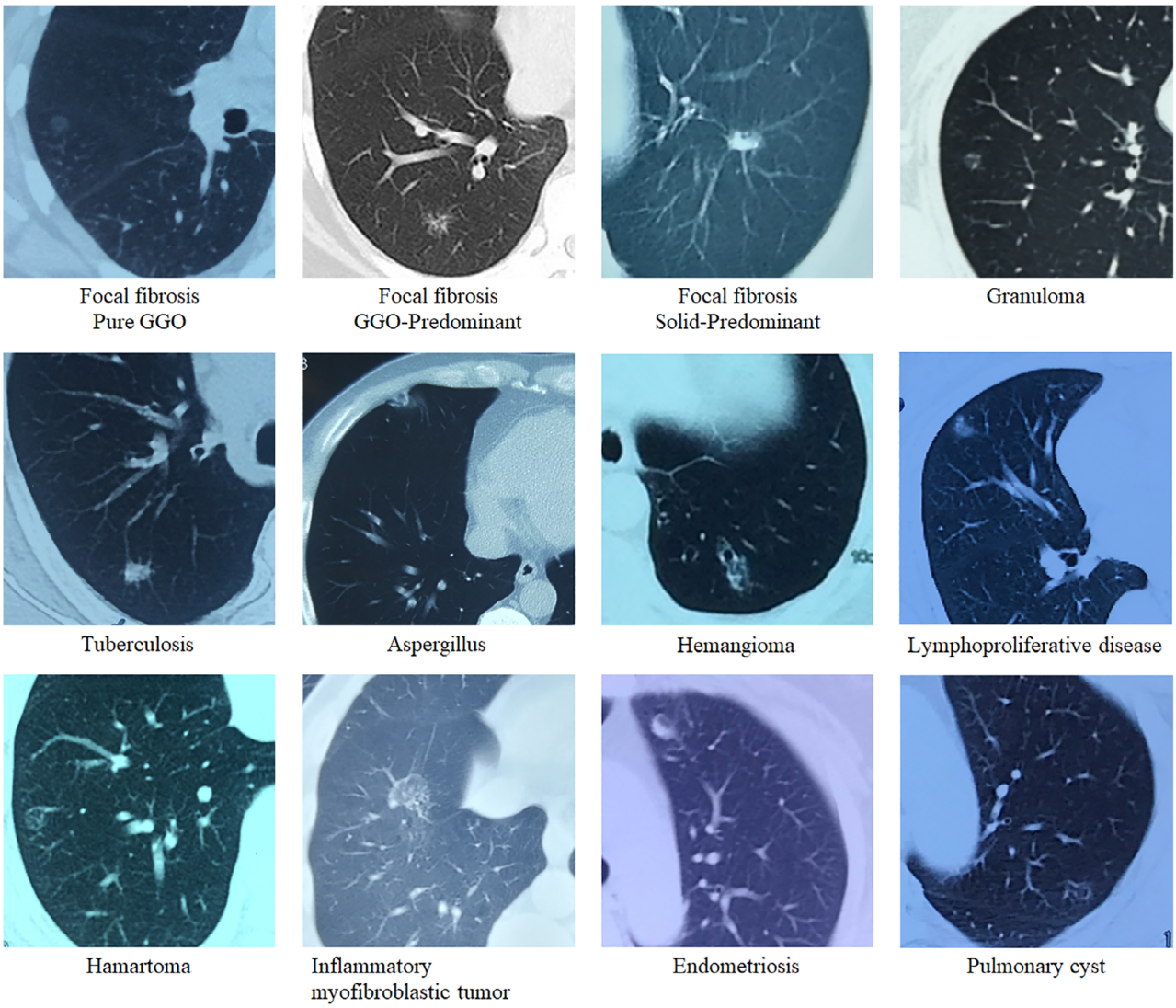

Figure 2 CT images of benign GGOs.

that showed between-group differences in our study. This is consistent with studies conducted in solid tumors.[15] However, it was suggested that air bronchogram signs could also be present in inflammatory nodules.[16] It is interesting that significantly more benign GGOs (80.0% vs. 57.1%) were located within 1 cm of the pleura. This might result from selection bias, as lesions located near the pleura were suitable for wedge resection. Although other CT features (spicule sign, vessel convergence sign, lobulated sign, calcifications, pleural indentation, thick/thin wall cavity, vacuole sign) are widely used to distinguish malignant solid tumors, we did not find between-group differences in our GGO series.

Bryan *et al.* reported that lung cancer was mostly located in the upper lobes (37% in the right upper lobe, 27% in the left upper lobe) after analyzing 13 650 cases, and the corresponding percentages were 15% in the right lower lobe and 14% in the left lower lobe. In our study, 78.6% of malignant GGOs were located in the upper and middle lobes, which was close to Bryan's data. However, a significantly lower proportion of benign GGOs were found in this location (57.1%). Extensive basic studies and large-scale clinical analyses are needed to explain this phenomenon.

Recent studies showed that PET/CT had an advantage in identifying MIA and IA among GGOs. In our study, PET/CT showed potential in identify malignant GGOs, as the sensitivity was 90.6% and the specificity was 42.1% after excluding uncertain patients. Nonetheless, the proportion of uncertain patients was so high that the clinical value of PET/CT remains to be determined.

Sufficient studies have discovered the population at high risk for solidary nodules, that is, asymptomatic patients aged

 © 2020 The Authors. *Thoracic Cancer* published by China Lung Oncology Group and John Wiley & Sons Australia, Ltd

55 to 80 years with a 30 pack-year smoking history who currently smoke or have quit within the previous 15 years. In our study, females accounted for 68.6% of the benign group, slightly exceeding than that reported for lung adenocarcinoma (62%). No differences in smoking history were found between the benign and malignant groups, although heavier smokers were found in the malignant group. Cough was the only manifestation with between-group differences and was less frequent in the benign group. It is slightly surprising that the incidences of all comorbidities were similar between the two groups, as we initially thought patients with comorbidities such as diabetes would be more susceptible to infection or inflammation. Our study also shows that antibiotics are not necessary, as there was no difference in anti-inflammatory therapy between the two groups.

Several guidelines on management strategies for GGOs have already been published. In the Fleischner Society guidelines, and resection is recommended for high-risk GGOs when solid components or growth is observed.[17] In the National Comprehensive Cancer Network (NCCN) guidelines, resection is recommended only when GGO growth or changes are observed.[18] The rationale for CT surveillance is that even if the GGOs are malignant, the incidence of IA is low,[19] and delayed surgery typically does not affect prognosis.[20, 21] However, these guidelines are usually based on Western populations. Preliminary evidence from many Asian studies suggest a possibly higher rate of malignancy or malignant potential among GGOs.[21–24] It is believed that if surgery can be conducted before progression, the long-term survival rate can reach 100%.[21, 25, 26] Therefore, surgeons in East Asia tend to be slightly more aggressive in terms of offering surgery.[23, 27] In clinical practice, we would actively consider surgery when the GGO is suspected to be malignant, even when some are unchanged during follow-up. The present retrospective study shows that only 35 out of 692 cases (5.1%) were benign GGOs. The incidence of malignant GGOs in our study was much higher than that reported in Western countries (usually 70% to 89%).[26]

Furthermore, previous studies suggested that the pathology of GGOs was usually AIS, MIA or LPA, all of which have good prognoses. However, studies in East Asia have suggested that GGOs can be associated with non-LPA,[28–30] and they have poorer prognoses. In our study, as many as 23 cases (32.9%) of non-LPA were found. This also supports our opinion on active surgery.

Three patients with benign GGOs underwent surgery even though the size decreased during follow-up. This might be because the GGOs were still considered to have a possibility of malignancy on imaging, and the size reduction was regarded as absorption of the surrounding inflammation. However, none of the malignant GGOs shrank during follow-up in our study. We thus suggest that when GGOs shrink, CT surveillance should be continued even if the nodule appears high risk on imaging.

In our study, the overall accuracy of intraoperative FS was 89.0%, slightly exceeding than that for solid tumors (84.4%).[26] However, there were still two patients in the benign group and nine patients in the malignant group who were treated with an improper resection strategy due to inaccurate intraoperative FS results. This suggests that the accuracy of intraoperative FS should be improved.

Our study has several limitations. First, we used a retrospective study design. Second, selection bias may be present, as GGOs with benign tendencies were excluded in outpatient evaluations. This makes it difficult to determine the clinical characteristics that would help in the differential diagnosis, as the enrolled benign GGOs highly resemble malignant GGOs. Third, the preoperative follow-up time in our study was shorter than that recommended by the existing guidelines. Several reasons may account for this: (i) some (25.7%) GGOs became larger during follow-up; (ii) some GGOs highly resembled cancer (i.e., 71.4% of GGOs contained a solid component); and (iii) some patients were very anxious and eager for resection of the GGOs. Additionally, the data were from a single institution, and the number of patients was relatively small.

In conclusion, our study shows that a higher smoking index, coughing, large size, unchanged or increased size during follow-up, location in the upper and middle lobes, air bronchogram sign on CT, lesion-margin-to-pleura distance of over 1 cm and malignant tendency on PET/CT were associated with malignant GGOs. However, classifying GGOs as malignant or benign is still difficult, especially when they are highly suspected to be malignant in outpatient evaluations. We thus recommend a relatively active surgical strategy, as the proportion of benign GGOs was small in resected nodules, and the degree of malignancy was not low. Further prospective and multicenter studies may provide more accurate results.

Acknowledgments

We thank all the staff members, statistical analysts, and quality control members who participated in the study.

Disclosure

The authors confirm that there are no conflicts of interest.

References

1 Moon Y, Sung SW, Lee KY, Park JK. Clinicopathological characteristics and prognosis of non-lepidic invasive adenocarcinoma presenting as ground glass opacity nodule. *J Thorac Dis* 2016; **8** (9): 2562–70.

 © 2020 The Authors. *Thoracic Cancer* published by China Lung Oncology Group and John Wiley & Sons Australia, Ltd

2 Fan L, Liu SY, Li QC, Yu H, Xiao XS. Multidetector CT features of pulmonary focal ground-glass opacity: Differences between benign and malignant. *Br J Radiol* 2012; **85** (1015): 897–904.
3 Beasley MB, Brambilla E, Travis WD. The 2004 World Health Organization classification of lung tumors. *Semin Roentgenol* 2005; **40** (2): 90–7.
4 Galateau-Salle F, Churg A, Roggli V, Travis WD. World Health Organization Committee for tumors of the Pleura. The 2015 World Health Organization classification of tumors of the pleura: Advances since the 2004 classification. *J Thorac Oncol* 2016; **11** (2): 142–54.
5 Kalra MK, Maher MM, Rizzo S, Kanarek D, Shepard JA. Radiation exposure from chest CT: Issues and strategies. *J Korean Med Sci* 2004; **19** (2): 159–66.
6 Lee HJ, Lee CH, Jeong YJ *et al.* IASLC/ATS/ERS international multidisciplinary classification of lung adenocarcinoma: Novel concepts and radiologic implications. *J Thorac Imaging* 2012; **27** (6): 340–53.
7 Gao JW, Rizzo S, Ma LH *et al.* Pulmonary ground-glass opacity: Computed tomography features, histopathology and molecular pathology. *Transl Lung Cancer Res* 2017; **6** (1): 68–75.
8 Mironova V, Blasberg JD. Evaluation of ground glass nodules. *Curr Opin Pulm Med* 2018; **24** (4): 350–4.
9 McGuinness G, Scholes JV, Garay SM, Leitman BS, McCauley DI, Naidich DP. Cytomegalovirus pneumonitis: Spectrum of parenchymal CT findings with pathologic correlation in 21 AIDS patients. *Radiology* 1994; **192** (2): 451–9.
10 Kim DS, Lee M, Kwon OJ *et al.* A 45-year-old man with recurrent dyspnea and hemoptysis during exercise: Exercise-induced pulmonary hemorrhage/edema. *Tubercul Respir Dis* 2015; **78** (4): 375–9.
11 Usui K, Ochiai T, Muto R *et al.* Diffuse pulmonary hemorrhage as a fatal complication of Schonlein-Henoch purpura. *J Dermatol* 2007; **34** (10): 705–8.
12 Hu H, Wang Q, Tang H, Xiong L, Lin Q. Multi-slice computed tomography characteristics of solitary pulmonary ground-glass nodules: Differences between malignant and benign. *Thorac Cancer* 2016; **7** (1): 80–7.
13 Sawada S, Yamashita N, Sugimoto R, Ueno T, Yamashita M. Long-term outcomes of patients with ground-glass opacities detected using CT scanning. *Chest* 2017; **151** (2): 308–15.
14 Migliore M, Fornito M, Palazzolo M *et al.* Ground glass opacities management in the lung cancer screening era. *Ann Transl Med* 2018; **6** (5): 90.
15 Farooqi AO, Cham M, Zhang L *et al.* Lung cancer associated with cystic airspaces. *AJR Am J Roentgenol* 2012; **199** (4): 781–6.
16 Kohno N, Ikezoe J, Johkoh T *et al.* Focal organizing pneumonia: CT appearance. *Radiology* 1993; **189** (1): 119–23.
17 MacMahon H, Naidich DP, Goo JM *et al.* Guidelines for management of incidental pulmonary nodules detected on CT images: From the Fleischner Society 2017. *Radiology* 2017; **284** (1): 228–43.
18 Ettinger DS, Wood DE, Aggarwal C *et al.* NCCN guidelines insights: Non-small cell lung cancer, version 1 2020. *J Natl Compr Cancer Netw* 2019; **17** (12): 1464–72.
19 Chen Ke-Neng. The diagnosis and treatment of lung cancer presented as ground-glass nodule. *General Thoracic and Cardiovascular Surgery*. 2019; http://dx.doi.org/10.1007/s11748-019-01267-4.
20 Callister ME, Baldwin DR, Akram AR *et al.* British Thoracic Society guidelines for the investigation and management of pulmonary nodules. *Thorax* 2015; **70** (Suppl 2): ii1–ii54.
21 Sihoe ADL, Cardillo G. Solitary pulmonary ground-glass opacity: Is it time for new surgical guidelines? *Eur J Cardio-Thorac Surg* 2017; **52** (5): 848–51.
22 Zhou Q, Fan Y, Wu N *et al.* Demonstration program of population-based lung cancer screening in China: Rationale and study design. *Thorac Cancer* 2014; **5** (3): 197–203.
23 Nawa T, Nakagawa T, Mizoue T, Endo K. Low-dose computed tomography screening in Japan. *J Thorac Imaging* 2015; **30** (2): 108–14.
24 Moon Y, Sung SW, Lee KY, Sim SB, Park JK. Pure ground-glass opacity on chest computed tomography: Predictive factors for invasive adenocarcinoma. *J Thorac Dis* 2016; **8** (7): 1561–70.
25 Sihoe AD, Van Schil P. Non-small cell lung cancer: When to offer sublobar resection. *Lung Cancer* 2014; **86** (2): 115–20.
26 Chen D, Dai C, Kadeer X, Mao R, Chen Y, Chen C. New horizons in surgical treatment of ground-glass nodules of the lung: Experience and controversies. *Ther Clin Risk Manag* 2018; **14**: 203–11.
27 Shi Z, Chen C, Jiang S, Jiang G. Uniportal video-assisted thoracic surgery resection of small ground-glass opacities (GGOs) localized with CT-guided placement of microcoils and palpation. *J Thorac Dis* 2016; **8** (7): 1837–40.
28 Son JY, Lee HY, Kim JH *et al.* Quantitative CT analysis of pulmonary ground-glass opacity nodules for distinguishing invasive adenocarcinoma from non-invasive or minimally invasive adenocarcinoma: The added value of using iodine mapping. *Eur Radiol* 2016; **26** (1): 43–54.
29 Liu LH, Liu M, Wei R *et al.* CT findings of persistent pure ground glass opacity: Can we predict the invasiveness? *Asian Pac J Cancer Prev* 2015; **16** (5): 1925–8.
30 Jin X, Zhao SH, Gao J *et al.* CT characteristics and pathological implications of early stage (T1N0M0) lung adenocarcinoma with pure ground-glass opacity. *Eur Radiol* 2015; **25** (9): 2532–40.

Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Table S1 Descriptions of the variables included in Table 1.
Table S2 Shapiro-Wilk test results for the continuous variables among clinical characteristics.
Table S3 Comparison of the involved lobes with GGOs.
Table S4 Accuracy of FS pathology for GGOs.

 © 2020 The Authors. *Thoracic Cancer* published by China Lung Oncology Group and John Wiley & Sons Australia, Ltd