Ground glass opacities: Imaging, pathology, and gene mutations

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ABSTRACT

Background: Lung cancer can be detected in its early stages with computed tomography (CT). Early lung adenocarcinoma often is displayed as ground glass opacity (GGO), an entity that has been well studied over the past decade. However, few studies have focused on the correlation between CT characteristics and pathologic subtype of GGO. We aimed to explore the correlation between CT characteristics, pathologic subtype, and gene mutation associated with GGO in an effort to aid in the treatment of lung adenocarcinoma.

Methods: In this retrospective study, patients with GGO who underwent surgery in our institution between 2013 and 2016 were included. Patients were divided into 2 groups on the basis of CT characteristics: group 1, diameter <20 mm and solid component <50%; and group 2, diameter ≥20 mm or solid component ≥50%. Differences in pathologic subtype and gene mutation pattern between groups were compared using the χ^2 test. The correlation between pathologic subtype and epidermal growth factor receptor (*EGFR*) mutation was also tested using the χ^2 test.

Results: A total of 1018 cases (408 in group 1, 610 in group 2) were included; of these, 544 were tested for the *EGFR* gene mutation. There was a significant difference in predominant subtype ($P < .001$) and all included subtypes ($P = .044$) between the groups. Of 59 cases with the pathologic subtype of micropapillary or solid, 57 were in group 2. The *EGFR* gene mutation rate was significantly higher in group 2 than group 1 ($P < .001$) and significantly correlated with pathologic subtype ($P < .001$); adenocarcinoma in situ was the lowest (31.4%) and papillary was the highest (85.7%). *EGFR* mutation subtype did not significantly differ between groups ($P = .499$).

Conclusions: CT characteristics of GGO significantly correlated with pathologic subtype and gene mutation rate. The *EGFR* mutation rate differed significantly among pathologic subtypes. GGOs with a diameter of <20 mm and with a solid component <50% seldom contain subtypes with poor prognosis (micropapillary and solid) and the *EGFR* mutation rate was significantly lower. (J Thorac Cardiovasc Surg 2018;156:808-13)

All pathologic subtypes in both groups.

Central Message

CT characteristics of GGO significantly correlated with pathologic subtype and gene mutation rate. Small GGOs seldom contain subtypes with poor prognosis.

Perspective

The *EGFR* mutation rate differed significantly among pathologic subtypes. Small GGOs seldom contain subtypes with poor prognosis. GGOs with a diameter <20 mm and a solid component <50% are more appropriate for sublobar resection than those with a diameter >20 mm and a solid component >50%.

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With the help of modern radiologic techniques, especially computed tomography (CT), lung cancer can be detected in its early stages. On CT scans, early lung cancer is often displayed as ground glass opacity (GGO). Pathologies of GGO are commonly associated with lung adenocarcinoma.¹

Scanning this QR code will take you to a supplemental video for the article.

Abbreviations and Acronyms

AIS	= adenocarcinoma in situ
CT	= computed tomography
<i>EGFR</i>	= epidermal growth factor receptor
GGO	= ground glass opacity
MIA	= microinvasive adenocarcinoma
NCCN	= National Comprehensive Cancer Network

In 2011, a new international multidisciplinary classification system for lung adenocarcinoma was proposed by the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society.² The histological subtype has significant influence on prognosis. Micropapillary and solid subtypes are correlated with poor prognosis.³⁻⁵ According to National Comprehensive Cancer Network (NCCN) guidelines, nodules <2 cm and ≥50% ground glass appearance is the indication for sublobar resection. However, few studies have explored the correlation of imaging characteristics, pathologic subtype, and gene mutation in GGO. Somatic mutations of epidermal growth factor receptor (*EGFR*) are found in a significant proportion of lung adenocarcinoma.⁶ Still, the association between clinical and pathologic characteristics and subtypes of the *EGFR* mutation in GGO has not been well evaluated. In this study, we aimed to explore this association to investigate the NCCN guidelines for sublobar resection from a histological and gene perspective and hopefully aid in the treatment of lung adenocarcinoma.

METHODS

This study protocol was approved by the Ethics Committee of Zhongshan Hospital, Fudan University, Shanghai, China (approval number B2017-115). Written informed consent was obtained from all patients before surgery for the use of surgical samples and clinical information for medical research.

Patients

The indication of surgery for GGO patients were: (1) pure GGO >20 mm or mixed GGO ≥10 mm, (2) do not diminish during a 3-month follow-up, and (3) heart and lung function can tolerate surgery. We retrospectively reviewed the records of patients with GGO who underwent curative surgical resection at our institute between January 2013 and December 2016. Inclusion criteria were as follows: (1) pathologically confirmed primary lung adenocarcinoma or atypical adenomatous hyperplasia, and (2) R0 resection. Exclusion criteria were: (1) no pathologic subtype data, and (2) missing data. Sex, age, lesion diameter, diameter of the solid component, gene mutation, and pathologic subtype were analyzed.

Analysis of *EGFR* Mutation

Formalin-fixed, paraffin-embedded tissue sections of the resected tumors were used for the analysis of *EGFR* mutation. DNA extraction and analysis of exons 18, 19, 20, and 21 were performed using the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method by Mitsubishi Kagaku Bio-chemical Laboratories Inc (Tokyo, Japan).

TABLE 1. Clinical and pathologic characteristics of the 2 groups

	Group 1	Group 2	<i>P</i> value
Age, y	52 ± 0.56	59.2 ± 0.414	<.001
Sex, (%)			.068
Male	104 (10.22)	189 (18.57)	
Female	304 (29.86)	421 (41.36)	
Median of follow-up time before surgery, mo	4	2	
Progression during follow-up, (%)			.986
With progression	53 (5.21)	78 (7.66)	
Without progression	355 (34.87)	532 (52.26)	
Gene mutation test, (%)			.0006
Yes	196 (19.25)	348 (34.18)	
No	212 (20.83)	262 (25.74)	
Predominant subtype, (%)			<.001
AAH	7 (0.69)	1 (0.10)	
AIS	111 (10.90)	12 (1.18)	
MIA	203 (19.94)	145 (14.24)	
Lepidic	17 (1.67)	65 (6.39)	
Acinar	66 (6.48)	370 (36.35)	
Papillary	4 (0.39)	17 (1.67)	
All pathologic subtype, (%)			.017
AAH	7 (0.69)	1 (0.10)	
AIS	111 (10.90)	12 (1.18)	
MIA	203 (19.94)	145 (14.24)	
Lepidic	43 (4.22)	198 (19.45)	
Acinar	79 (7.76)	426 (41.85)	
Papillary	12 (1.18)	91 (8.94)	
Micropapillary	1 (0.10)	33 (3.24)	
Solid	1 (0.10)	24 (2.36)	
Gene mutation, (%)			<.001
Wild type	95 (17.46)	97 (17.83)	
<i>ALK</i>	0 (0.00)	1 (0.18)	
<i>B-RAF</i>	2 (0.37)	1 (0.18)	
<i>EGFR</i>	78 (14.34)	232 (42.65)	
<i>HER-2</i>	13 (2.39)	5 (0.92)	
<i>K-RAS</i>	4 (0.74)	6 (1.10)	
<i>PIK3CA</i>	0 (0.00)	1 (0.18)	
<i>RET</i>	3 (0.55)	2 (0.37)	
<i>ROS-1</i>	1 (0.18)	3 (0.55)	

AAH, Atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; MIA, microinvasive adenocarcinoma; *ALK*, anaplastic lymphoma kinase; *B-RAF*, B-rapidly accelerated fibrosarcoma; *EGFR*, epidermal growth factor receptor; *HER-2*, human epidermal growth factor receptor 2; *K-RAS*, Kirsten rat sarcoma viral oncogene homolog; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *RET*, ret proto-oncogene; *ROS-1*, c-ros oncogene 1 receptor tyrosine kinase.

CT Characteristics and Pathology

Thin-slice CT (1 mm per slice) was used to measure the GGO and consolidation component. GGO is defined as a misty increase in lung attenuation without obscuring the underlying vascular markings. The consolidation component is defined as an area of increased opacification that completely obscures the underlying vascular structures. The solid component ratio was calculated by dividing the maximum consolidation diameter by the maximum tumor dimension including ground glass part in the lung window. CT scans were reviewed and tumor sizes determined by 2

FIGURE 1. Predominant subtypes in both groups. *AAH*, Atypical adenomatous hyperplasia; *AIS*, adenocarcinoma in situ; *MIA*, microinvasive adenocarcinoma; *D*, diameter.

independent radiologists. Disagreements were resolved by consensus. Pathology and gene mutation results were acquired from pathology reports.

Statistical Analysis

Cases were separated into 2 groups on the basis of CT characteristics. Group 1 were patients with a diameter <20 mm and a solid component <50%. Group 2 included patients with a diameter of ≥20 mm or a solid component of ≥50%. Differences in pathologic subtype and gene mutation pattern between groups and the correlation between pathologic subtype and *EGFR* mutation were tested using the χ^2 test or Fisher exact test. Statistical analyses were performed using R software, version 3.3.1 (<http://www.r-project.org/>). A *P* value of < .05 was considered statistically significant.

RESULTS

A total of 1018 GGOs (408 in group 1, 610 in group 2) from 894 patients were included in this study. One hundred three patients had more than 1 GGO. As shown in Table 1, there was no significant difference between the 2 groups with regard to sex. There was a significant difference with regard to age between groups (52 ± 11.4 vs 59.2 ± 10.2 years; $P < .001$).

Correlation Between CT Characteristics and Pathologic Subtypes

Figure 1 shows the predominant subtypes in both groups. There were no cases of predominant subtypes with micropapillary or solid components in either group. Adenocarcinoma in situ (AIS) and microinvasive adenocarcinoma (MIA) accounted for most cases in group 1, whereas MIA and acinar accounted for a large part in

group 2. There was a statistically significant difference between groups with regard to predominant subtype ($P < .001$).

Then, we analyzed the difference of all pathologic subtypes between groups (Figure 2). As shown in Table 2, only 2 (2.3%) cases in group 1 had a micropapillary or solid component, versus 58 (12.9%) in group 2. The number of cases with micropapillary or solid components in group 2 was significantly more than that in group 1 ($P < .001$).

Correlation Between CT Characteristics and Gene Mutation

Not all cases were tested for gene mutations. Figure 3 shows the pattern of gene mutations in both groups. In both groups, the wild type and *EGFR* mutations comprised nearly 90% of cases. However, the *EGFR* mutation rate was significantly higher in group 2 than in group 1 ($P < .001$). The difference in the *EGFR* mutation site between groups was also tested (Figure 4). Mutations in exon 19 and 21 comprised most in both groups, without a significant difference between them ($P = .498$).

Correlation Between Pathologic Subtypes and *EGFR* Mutation

The following analysis was focused on the *EGFR* mutation, which is the most frequent mutation in lung adenocarcinoma. Figure 5 shows the correlation between the predominant pathologic subtype and the *EGFR* mutation.

FIGURE 2. All pathologic subtypes in both groups. *AAH*, Atypical adenomatous hyperplasia; *AIS*, adenocarcinoma in situ; *MIA*, microinvasive adenocarcinoma; *D*, diameter.

TABLE 2. Subgroup analysis of EGFR mutation rates of lepidic predominant cases

	With EGFR mutation	Without EGFR mutation
Lepidic predominant with other minor subtypes	21	6
Only lepidic subtype	3	6

EGFR, Epidermal growth factor receptor.

The EGFR mutation rate of AIS, MIA, lepidic, acinar, and papillary subtypes was 31.4%, 38.5%, 67.6%, 70.1%, and 85.7%, respectively ($P < .001$).

To determine the reason for the significant difference in EGFR mutation rate between MIA and lepidic subtypes, we further analyzed the latter (lepidic). As shown in Table 2, the EGFR mutation rate in lepidic subtypes was 33.3% (close to the EGFR mutation rate of MIA), compared with 77.8% in all other cases.

DISCUSSION

Today, GGO is becoming an increasingly common indication for lung surgery. However, the extent of surgery is quite controversial.⁷⁻¹¹ Wedge resection, segmentectomy, and lobectomy are all currently used to treat GGO. Video 1 shows a sublobar resection performed in our center. In this study, we separated all patients into 2 groups according to CT characteristics (diameter <20 mm and solid component <50% as group 1; diameter ≥20 mm or solid component ≥50% as group 2) and try to explore the differences in pathology and gene mutation patterns between these 2 groups. According to NCCN guidelines, the indication for sublobar resection is a peripheral nodule <2 cm in size with at least 1 of the following: (1) pure bronchioalveolar carcinoma histology, (2) nodule with ≥50% ground glass appearance on CT imaging, and (3) radiologic surveillance confirming a long doubling time (>400 days), and it is the reason that the 2 groups were separated at the cut point of 2 cm and 50% solid component.¹²

Most lung adenocarcinomas show heterogeneous histological patterns.¹³ In one lesion, there could be a

predominant subtype and several minor components. In this study, all pathologic subtypes were included to explore their correlation with CT characteristics. None of the cases in our cohort had predominant micropapillary or solid subtypes. As for all components, only 2.3% of group 1 patients had a micropapillary or solid component, a significantly lower rate than in group 2 (12.9%). A previous study showed that the prognosis for lepidic predominant adenocarcinoma in stage I patients was excellent, whereas that of the solid and micropapillary subtypes were poor.¹³⁻¹⁹ The presence of the micropapillary subtype was a poor prognostic factor.⁵ Moreover, our former study showed that the rate of lymph node metastasis was very low in peripheral lung cancers <20 mm in size.²⁰ Thus, lesions with a diameter <20 mm in size, and a solid component <50% have a better prognosis than those with a diameter >20 mm and with a solid component >50%.

An activated mutation of the EGFR gene was first reported in 2004.²¹⁻²³ Since then, the biologic and clinical characteristics of the EGFR mutation have been extensively studied.^{24,25} EGFR mutations are more prevalent in those of Asian ethnicity.^{24,25} It has been reported that 47% to 64% of patients from East Asian regions with lung adenocarcinomas harbored EGFR mutations.²⁶ However, most studies focused on advanced lung adenocarcinoma. In this study, we analyzed the gene mutation pattern in early stage lung adenocarcinoma. According to our results, 39.4% of cases in group 1 and 66.7% of those in group 2 harbored EGFR mutations, consistent with previous studies²⁶ and the difference between the groups was statistically significant ($P < .001$). Furthermore, we also analyzed EGFR mutations in different pathologic subtypes. The EGFR mutation rate was 30% to 40% in AIS and MIA subtypes, but as high as 70% to 80% in lepidic, acinar, and papillary subtypes. Because MIA was defined as a ≤3 cm lepidic predominant tumor with ≤5-mm invasion, we investigated why the EGFR mutation rate was much higher than that in MIA. Our results showed that the EGFR mutation rate of lesions with only the lepidic component was significantly higher than that of other components.

FIGURE 3. Gene mutation pattern in both groups. B-RAF, B-rapidly accelerated fibrosarcoma; EGFR, epidermal growth factor receptor; HER-2, human epidermal growth factor receptor 2; K-RAS, Kirsten rat sarcoma viral oncogene homolog; RET, ret proto-oncogene; ROS-1, c-ros oncogene 1 receptor tyrosine kinase; D, diameter; ALK, anaplastic lymphoma kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

FIGURE 4. *EGFR* mutation site in both groups. *EGFR*, Epidermal growth factor receptor; *D*, diameter.

This result indicates that the *EGFR* mutation rate was lower in cancers with lepidic components but higher in those with acinar and papillary components. These results imply that *EGFR* mutations not only function in tumor genesis²⁷ but are also generated during tumor development. In the era before targeted therapy, which was seldom used in early-stage lung adenocarcinoma, *EGFR* overexpression correlated with a poor prognosis.²⁸⁻³⁰

Besides size and solid component, the prognostic value of other factors such as pleural tag, presence or absence of lobulation, and air bronchogram has been evaluated extensively.³¹⁻³⁴ However, the studies came to truly mixed results. Moreover, these factors are rather subjective and hard to quantify. Therefore, these factors were not considered in the study. There are several limitations of this study. First, only patients from a single center were included in this study. Our results need to be further validated in a multicenter study. Because *EGFR* mutation rate is different between East ethnicity and West ethnicity,

how *EGFR* mutation and pathologic subtypes are correlated in West population needs further research. Second, the 2 groups were not completely homogeneous in age and this might cause bias and influence the results. Third, not all patients were tested for *EGFR* mutation and not all GGO patients received surgery. This nonrandom and systematic difference in missing *EGFR* status between groups highly biases the results of the analyses. Therefore, a prospective, randomized study is needed to further validate our results. Fourth, no long-term data were analyzed in this study. Discussions regarding prognosis were on the basis of indirect evidence of other studies. To further explore this issue, a long-term follow-up is needed.

CONCLUSIONS

GGOs with a diameter of <20 mm and a solid component of <50% differs significantly from GGOs with a diameter >20 mm or a solid component of >50% in pathology and gene mutation patterns. The *EGFR* mutation rate varies significantly in cases with different predominant subtypes.

FIGURE 5. Correlation between the predominant pathologic subtype and *EGFR* mutation rate. *EGFR*, Epidermal growth factor receptor; AIS, adenocarcinoma in situ; MIA, microinvasive adenocarcinoma. *** $P < .001$; # $P > .05$.

VIDEO 1. Segmentectomy of left upper lobe S1 + 2 + 3. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)30941-3/fulltext](https://www.jtcvs.org/article/S0022-5223(18)30941-3/fulltext).

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: GGO, imaging characteristics, pathologic subtype, *EGFR* mutation