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# Discrepancy of epidermal growth factor receptor mutation in lung adenocarcinoma presenting as multiple ground-glass opacities

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## Abstract

**OBJECTIVES:** To identify epidermal growth factor receptor (EGFR) mutation status between different lesions in lung adenocarcinoma presenting as multiple ground-glass opacity (GGO) lesions and analyse its association with clinical characteristics.

**METHODS:** Seventy-eight patients with lung adenocarcinoma presenting as multiple GGO lesions were identified to investigate EGFR mutation in exon 18–21. Lesions with the largest size in diameter were defined as the primary lesions; the others were defined as the secondary lesions. One hundred and fifty-nine lesions of these patients were classified into pure GGO and mixed GGO by computed tomography scan images.

**RESULTS:** The EGFR mutation rate in the patients was 48.7% (38 of 78). Patients with high frequency of EGFR mutation were females and non-smokers. The EGFR mutation rate of invasive adenocarcinoma was higher than that of atypical adenomatous hyperplasia/adenocarcinoma *in situ* and minimally invasive adenocarcinoma ( $P = 0.001$ ). Although 19-deletion and L858R were the most common EGFR mutations, there was no difference of EGFR mutation in pathological subtypes of adenocarcinoma. Of the 38 paired lesions in patients harbouring EGFR mutation, the discordance rate of EGFR mutation was 92.1%.

**CONCLUSIONS:** The study showed different EGFR mutational profiles in multiple GGO lesions, suggesting that lesions seem to arise as independent events. It would offer useful information for determining the appropriate treatment strategy for lung adenocarcinoma presenting as multiple GGO lesions.

**Keywords:** Synchronous multiple primary lung cancers • Ground-glass opacities • EGFR • Surgery

## INTRODUCTION

The incidence of lung cancer with multiple ground-glass opacity (GGO) lesions is increasing as the result of the widespread use of multislice spiral computed tomography (CT) and the low-dose CT screening for lung cancer detection. Usually, a persistent GGO lesion at CT is strongly suggestive of a neoplastic condition, such as atypical adenomatous hyperplasia (AAH), adenocarcinoma *in situ* (AIS) or minimally invasive adenocarcinoma (MIA) [1–3]. Although the molecular test was recommended in patients with advanced lung adenocarcinoma, it is recognized that EGFR mutation testing may be performed in patients with early-stage disease. In addition, other molecular tests, such as KRAS and EML4-ALK, were also performed in many institutions. EGFR mutation was found in the early stage of lung adenocarcinoma, such as AAH and AIS. It is suggested that EGFR mutation might play an important role in disease progression, especially in lung adenocarcinoma. Nevertheless, the EGFR mutation status between multiple GGO lesions of lung

adenocarcinoma was seldom studied. Therefore, the purpose of this retrospective study was to identify EGFR mutation status between multiple GGO lesions in surgically resected lung adenocarcinoma stratified by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) classification in a Chinese cohort of patients.

## MATERIALS AND METHODS

### Patients

This study was approved by the Institutional Review Board of the Shanghai Pulmonary Hospital and the written informed consent was given by all participants for their clinical records to be used in this study. From January 2013 to January 2014, a total of 818 cases of lung adenocarcinoma that underwent surgery were identified, including 301 cases presented as GGO and 78 patients presented as multiple GGO lesions. All patients did not receive any therapy for lung cancer before surgery. The tumor, node, and metastasis (TNM)

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stage was determined by the highest stage of all lesions according to the seventh TNM classification guidelines. Pathological subtypes were classified according to the IASLC/ATS/ERS guidelines published in 2011. Prospectively collected demographic variables included age, sex, smoking status, stage, location, pathological subtypes, tumour size, surgical type and tumour density. The largest lesion size in diameter was used for the assessment of GGO growth by low-dose multislice spiral CT. Consolidation tumour ratio (CTR) was used in this study according to the published studies and patients were divided into pure GGO group and mixed GGO group ( $0 < \text{CTR} \leq 0.5$ ) [4–6]. Management for GGO was recommended by Fleischner Society and American College of Chest Physicians [7, 8]: Pure GGO measuring  $\leq 5$  mm requires an initial follow-up CT examination every 2 years; mixed GGO measuring  $\leq 5$  requires an initial follow-up CT examination at 6 months, then subsequently annual surveillance CT for a minimum of 3 years; pure GGO measuring  $>5$  to 8 mm requires an initial follow-up CT examination at 3 months, then subsequently annual surveillance CT for a minimum of 3 years, biopsy or surgical resection is recommended if enlarged; mixed GGO measuring  $>5$  to 8 mm requires an initial follow-up CT examination at 3 months, if persistent or enlarged, biopsy or surgical resection is recommended; GGO measuring  $\geq 8$  mm requires an initial follow-up CT examination at 3 months, if persistent or enlarged, biopsy or surgical resection is recommended. The benign diseases and the benign lesions in multiple GGO lesions were excluded from the study.

Tissue samples and mutation analysis

Genomic DNA was extracted from fresh tissues using QIAamp DNA Tissue Kit (Qiagen, Germany). EGFR mutation was detected using commercially available kits from Amoy Diagnostics (Xiamen, China) based on amplification refractory mutation system real-time polymerase chain reaction technology. Twenty-nine kinds of EGFR mutation in exon 18–21 were detected in all lesions of these patients.

Statistical analysis

The descriptive statistics for categorical variables are reported as frequencies and percentages and continuous variables as

mean  $\pm$  standard deviation. Nominal categorical variables were compared using the  $\chi^2$  test. Logistic regression model was used for multivariable analysis to determine whether gender, smoking status and tumour size independently predict EGFR mutation. All analysis was performed with SPSS for Windows (Version 13.0, Chicago, IL, USA). *P*-values less than 0.05 were considered to be statistically significant.

RESULTS

The study included 51 cases of Stage Ia disease and 27 cases of Stage Ib disease. The mean age was  $58.03 \pm 9.10$  years. The demographic characteristics and EGFR mutation in patients are given in Table 1. A total of 159 lesions with mean largest lesion size in diameter of  $2.23 \pm 0.91$  cm were identified in 78 patients; two lesions were present in 75 patients and three lesions were present in 3 patients. Surgical procedures for 78 patients with multiple GGO lesions are illustrated in Table 2. Synchronous bilateral surgery was performed in 27 cases and metachronous bilateral surgery was performed in 8 patients because of the threshold value of pulmonary function (5 cases) and unexpected accident during the first surgery (3 cases). The second surgery was performed after reassessment in 1–2 months after the first surgery.

The EGFR mutation rate in the patients was 48.7% (38 of 78). Higher frequency of EGFR mutation was found in females ( $\chi^2 = 5.673$ ,  $P = 0.017$ ) and non-smokers ( $\chi^2 = 7.866$ ,  $P = 0.005$ ). In multivariable analysis for predicting EGFR mutation, sex [odds ratio: 4.352, 95% confidence interval (CI): 1.274–14.870] and smoking status (odds ratio: 3.599, 95% CI: 1.083–11.956) were independent predicting factors for EGFR mutation. However, age, location and largest lesion size were not independently predicting factors for EGFR mutation.

The detail of EGFR mutation in 159 lesions is summarized in Table 3. EGFR mutation rate of invasive adenocarcinoma was higher than that of AAH/AIS and MIA ( $\chi^2 = 14.602$ ,  $P = 0.001$ ). Although 19-deletion and L858R were the most common EGFR mutations, there was no difference of EGFR subtype mutation in pathological subtypes of adenocarcinoma. In addition, no difference of EGFR mutation was found between pure GGO and mixed GGO.

Table 1: Demographic characteristics and EGFR mutation in 78 patients presenting as multiple GGO lesions

	Total	Mutation, n (%)	Wild, n (%)	$\chi^2$	P-value
Age (years)					
≤60	41	22 (53.7)	19 (46.3)	0.479	0.489
>60	37	16 (43.2)	21 (56.8)		
Sex					
Male	30	9 (30.0)	21 (70.0)	5.673	0.017
Female	48	29 (60.4)	19 (39.6)		
Smoking status					
Smoker	32	9 (28.1)	23 (71.9)	7.866	0.005
Non-smoker	46	29 (63.0)	17 (37.0)		
Location					
Unilateral	43	17 (39.5)	26 (60.5)	2.467	0.116
Bilateral	35	21 (60.0)	14 (40.0)		
Largest lesion size					
≤3 cm	49	26 (53.1)	23 (46.9)	0.582	0.445
>3 cm	29	12 (41.4)	17 (58.6)		

GGO: ground-glass opacity; EGFR: epidermal growth factor receptor.

Because the patients who were presented as three GGO lesions were all wild type in EGFR gene, a total of 53 mutations were identified in 76 lesions of 38 patients who each had two lesions. The lesion with the larger size in diameter was defined as the primary lesion, the other was defined as the secondary lesion. Different histology between the primary and secondary lesions was found in 56 patients and the same histology was found in 22 patients. Both the primary and secondary lesions were diagnosed as invasive adenocarcinomas in 8 patients and MIA in 14 patients. The EGFR mutations between the primary and secondary lesions are presented in Table 4. Among the 38 paired lesions, 92.1% (35) of paired lesions presented different EGFR mutation status, including 23 cases with mutation in one lesion and 12 cases with different mutation in the primary and secondary lesions. Only 3 cases with identical mutation presented identical EGFR mutation status. No difference was found in the distribution of EGFR subtype mutation between the primary and secondary lesions.

## DISCUSSION

In this study, we investigated EGFR mutation status in 159 lesions from 78 patients to determine the discrepancy of mutation in lung adenocarcinoma patients presented as multiple GGO lesions. To the best of our knowledge, this is the first study to investigate the EGFR mutation between lesions in a cohort of lung adenocarcinoma patients with multiple GGO lesions. We found a high discordance rate of 92.1% in paired lesions of 38 patients harbouring EGFR mutation.

**Table 2:** Surgical procedures for 78 patients with multiple GGO lesions

Unilateral	Cases (n = 43)	Bilateral	Cases (n = 35)
Wedge resection	6	Bilateral wedge resection	7
Segmentectomy	5	Bilateral segmentectomy	4
Lobectomy	15	Bilateral lobectomy	6
Lobectomy + wedge/segmentectomy	17	Lobectomy + wedge/segmentectomy	18

GGO: ground-glass opacity.

EGFR mutation was an early event in lung adenocarcinoma and was significantly associated with invasion. Having benefited from the low-dose CT screening for lung cancer detection, more patients with early-stage lung cancer were found. The initial finding of CT in these patients often presented as GGO lesion and the diagnoses of these GGO lesions were mostly AAH, AIS or MIA, in which EGFR mutation had been found [9–11]. With the increase of solid proportion in GGO, AIS and MIA were shown to have a decreasing trend, whereas invasive adenocarcinoma exhibited an increasing trend. In our study, the most common pathological subtype was MIA followed by invasive adenocarcinoma and AAH/AIS. EGFR mutation was found in 38 (48.7%) of the 78 patients, and 19-deletion and L858R were the most common EGFR mutations. As expected, patients with high frequency of EGFR mutation were females and non-smokers. EGFR mutation rate of invasive adenocarcinoma was higher than that of AAH/AIS and MIA. The result concurred with the hypothesis for the progression of lung adenocarcinoma that EGFR-mutated AAH follows a linear progression schema, whereby AAH progresses to AIS and is followed by MIA [12, 13]. Because the high proportion of GGO in lung adenocarcinomas is well known to be an indicator of better prognosis [14], EGFR mutation is an early event in the pathogenesis of lung adenocarcinoma and may facilitate the lesion into aggressive behaviour.

GGO features, including GGO proportion, tumour volume and diameter, were correlated with EGFR mutation. In our study, although more 19-deletion and L858R mutation were found in mixed GGO, there was no significant difference of EGFR mutation between pure GGO and mixed GGO. A lack of further study stratified by GGO features may account for our results. Some studies showed that tumour volume and diameter were correlated with L858R mutation and GGO proportion was correlated with 19-deletion mutation or L858R mutation [9, 10, 15]. In line with previous reports, EGFR mutation is associated with the invasive adenocarcinoma in our study. It seems that multiple GGO lesions have a similar EGFR profile mutation to single GGO and the more GGO proportion of lesion had less typical EGFR mutation. It supported the result of higher EGFR mutation in invasive adenocarcinoma, which usually presents more solid proportion.

The relationship of gene mutation status between multiple GGO lesions in lung adenocarcinoma was seldom studied. Wu et al. [16] reported a discordance rate of 80% in patients harbouring at least one of the detected driver mutations in non-small-cell lung cancer (NSCLC). Limitations were the small number of cases, diversity of histology and low mutation rate in detected driver mutation except EGFR. Because of high EGFR mutation rate in Asian populations, we focused on subtypes of EGFR mutation in

**Table 3:** EGFR mutation in 159 lesions of 78 patients with multiple GGO lesions

	Total (n)	AAH/AIS, n (%)	MIA, n (%)	IV, n (%)	$\chi^2$	P-value	Pure GGO, n (%)	Mixed GGO, n (%)	$\chi^2$	P-value
Wild	106	22 (20.7)	57 (53.8)	27 (25.5)	14.602	0.001	47 (44.3)	59 (55.7)	0.729	0.393
Mutation	53	10 (18.9)	14 (26.4)	29 (54.7)			19 (35.8)	34 (64.2)		
L858R	21	4 (19.1)	7 (33.3)	10 (47.6)	3.314	0.769	9 (42.9)	12 (57.1)	0.960	0.811
19-del	24	4 (16.7)	4 (16.7)	16 (66.6)			7 (29.2)	17 (70.8)		
L858R/19-del	5	1 (20.0)	2 (40.0)	2 (40.0)			2 (40.0)	3 (60.0)		
Other	3	1 (33.3)	1 (33.3)	1 (33.3)			1 (33.3)	2 (66.7)		

AAH: atypical adenomatous hyperplasia; AIS: adenocarcinoma *in situ*; MIA: minimally invasive adenocarcinoma; IV: invasive adenocarcinoma; GGO: ground-glass opacity; EGFR: epidermal growth factor receptor.

**Table 4:** Detail of EGFR mutation in the 38 paired lesions

No.	Primary lesions	Secondary lesions
1 <sup>a</sup>	E746_T751>I	Wild
2 <sup>b</sup>	L747_E749del	L858R
3 <sup>b</sup>	E746_A750del (1)	G719S
4 <sup>b</sup>	L858R	E746_A750del (1)
5 <sup>a</sup>	E746_A750del (2)	Wild
6 <sup>b</sup>	L858R	E746_A750del (2)
7 <sup>a</sup>	L858R	Wild
8 <sup>a</sup>	Wild	L858R
9 <sup>a</sup>	Wild	S768I
10 <sup>c</sup>	E746_A750del (1)	E746_A750del (1)
11 <sup>c</sup>	L858R	L858R
12 <sup>a</sup>	Wild	E746_A750del (1)
13 <sup>a</sup>	L858R	Wild
14 <sup>a</sup>	L858R	Wild
15 <sup>a</sup>	Wild	E746_A750del (1)
16 <sup>a</sup>	L858R	Wild
17 <sup>a</sup>	Wild	E746_A750del (1)
18 <sup>b</sup>	E746_A750del (2)	L858R
19 <sup>a</sup>	L858R	Wild
20 <sup>a</sup>	Wild	L858R
21 <sup>a</sup>	E746_A750del (1)	Wild
22 <sup>a</sup>	E746_A750del (1)	Wild
23 <sup>b</sup>	E746_A750del (2)	L858R
24 <sup>a</sup>	L858R	Wild
25 <sup>b</sup>	L858R	E746_A750del (2)
26 <sup>b</sup>	E746_A750del (1)	L858R
27 <sup>a</sup>	E746_A750del (1)	Wild
28 <sup>c</sup>	E746_A750del (2)	E746_A750del (2)
29 <sup>a</sup>	Wild	E746_A750del (1)
30 <sup>b</sup>	E746_A750del (2)	L858R
31 <sup>a</sup>	E746_A750del (2)	Wild
32 <sup>a</sup>	Wild	E746_A750del (1)
33 <sup>a</sup>	L858R	Wild
34 <sup>b</sup>	E746_A750del (2)	L858R
35 <sup>b</sup>	L858R	L747_P753>S
36 <sup>a</sup>	L861Q	Wild
37 <sup>a</sup>	L858R	Wild
38 <sup>b</sup>	L858R	L858R, E746_A750del (1)

<sup>a</sup>Mutation in only one lesion.  
<sup>b</sup>Different mutation in the primary and secondary lesions.  
<sup>c</sup>Identical mutation in the primary and secondary lesions.

multiple GGO lesions. In patients harbouring EGFR mutation, we found a high discordance rate of 92.1% in paired lesions. The result suggests that multiple GGO lesions in lung adenocarcinoma seem to arise from a different origin. However, one important issue that should be stressed is intratumour heterogeneity, which is due to anatomical selection or evolution over time. It was reported that EGFR mutation in NSCLC was found to display intratumour heterogeneity and spatial discordance in 6.3–30% of cases [17, 18]. Therefore, the diagnosis of multiple primary lung adenocarcinomas presenting as multiple GGO lesions cannot completely rely on different gene mutation status, but it may aid in the ability to differentiate between primary lung cancers and metastases and improve the accuracy of clinicopathological diagnosis.

Our study had several limitations. Firstly, gene mutation status obtained using EGFR mutation only represents a small part of the picture because whole genome or exome sequencing was not used. Secondly, we could not investigate EGFR mutation of GGO lesions that were followed up without surgical resection. Thirdly, the high frequency of EGFR mutation in the present study appears to be influenced by ethnic features.

In conclusion, EGFR mutation rate was higher in females, non-smokers and invasive adenocarcinomas. By the study of distribution of EGFR subtype mutation between the primary lesions and secondary lesions, we found a high discordance of EGFR mutation. Multiple GGO lesions in lung adenocarcinoma seem to arise from different origins and developed independently, and the findings would offer useful information for determining treatment strategy for lung adenocarcinoma presenting as multiple GGO lesions.

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**Conflict of interest:** none declared.

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## EDITORIAL COMMENT

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# Re: Discrepancy of epidermal growth factor receptor mutation in lung adenocarcinoma presenting as multiple ground-glass opacities

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**Keywords:** Synchronous multiple primary lung cancers • Ground-glass opacities • EGFR • Surgery

In this issue of the journal, the manuscript by Liu *et al.* [1] describes the epidermal growth factor receptor (EGFR) mutation status in resected lung lesions in patients with multiple ground-glass opacities (GGOs). The authors describe 78 patients who underwent resection of 159 GGOs, for which histological classification and EGFR mutation testing were performed on each resected lesion. The authors found an expected high rate (48.7%) of EGFR mutations in this cohort of Asian patients. Importantly, in paired lesions from patients with at least one EGFR mutation, there was a remarkable 92% discordance rate. Of the 38 pairs, 23 cases had mutations in only one lesion, whereas 12 pairs from the same patient had distinct EGFR mutations.

This is an important finding with critical implications for surgeons, but also for oncologists who deliver systemic therapy to patients with multiple ground-glass or part-solid nodules. The implication from this manuscript is that patients who may sometimes have the appearance of widespread, 'systemic' disease may in reality have multiple 'local' problems. This may be particularly applicable for patients with the disease confined to the thorax. Such an analysis fits with the emerging picture of EGFR mutational heterogeneity and the variable and often short-lived response to EGFR tyrosine kinase inhibitors (TKIs) that has been increasingly recognized in patients with metastatic disease [2]. The findings by Liu *et al.* suggest that

biopsies of more than one lesion should perhaps be obtained in patients with multiple GGOs when considering systemic therapy with TKIs. Furthermore, it raises the question of whether local therapy, either surgery or radiation, should be considered for some of these tumours, particularly those who do not respond to systemic therapy when other lesions clearly do. Such tumours may in fact simply be local problems, rather than systemic disease.

I applaud the authors on this important paper. As widespread mutation testing is more frequently adopted for early-stage tumours, we will continue to better understand the biological processes that drive lung cancer progression. There is a lot to be learned from early-stage tumours which can also undoubtedly be applied to the understanding of patients with metastatic disease.

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