

## Case Report

# Small-cell lung cancer transformation in a pulmonary adenocarcinoma patient as an acquired resistance mechanism to icotinib: a case report and review

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**Abstract:** Icotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), benefits patients with exon 19 deletion advanced non-small-cell lung cancer who have failed treatment with platinum-based chemotherapy. Acquisition of resistance to icotinib occurs inevitably and mechanisms need to be explored. We reported an advanced lung adenocarcinoma female with EGFR exon 19 deletion treated with icotinib after failure of gemcitabine plus cisplatin. Disease progressed again after 10 months' treatment of icotinib. Then the second bronchoscopy was performed and a histological examination confirmed histopathology transformation to small cell lung cancer, which harbored EGFR exon 19 deletion. Therefore, small cell carcinoma transformation is one of potential resistance mechanisms to icotinib and regimen for small cell carcinoma may be one of the treatment options. However, disease progressed after four cycles of etoposide plus carboplatin (EC) chemotherapy and adenocarcinoma emerged again. Amplification refractory mutation system (ARMS) analyses still revealed EGFR exon 19 deletions in third bronchoscopy biopsy. So the patient continued icotinib combined with EC chemotherapy and achieved good response. It is important for SCLC transformation patients to take the repeat biopsy after TKI resistance; Furthermore, patients with SCLC transformation may still benefit from classic anti-SCLC therapies and effective comprehensive treatment for the combined NSCLC component.

**Keywords:** NSCLC, icotinib, SCLC transformation, drug resistance

## Introduction

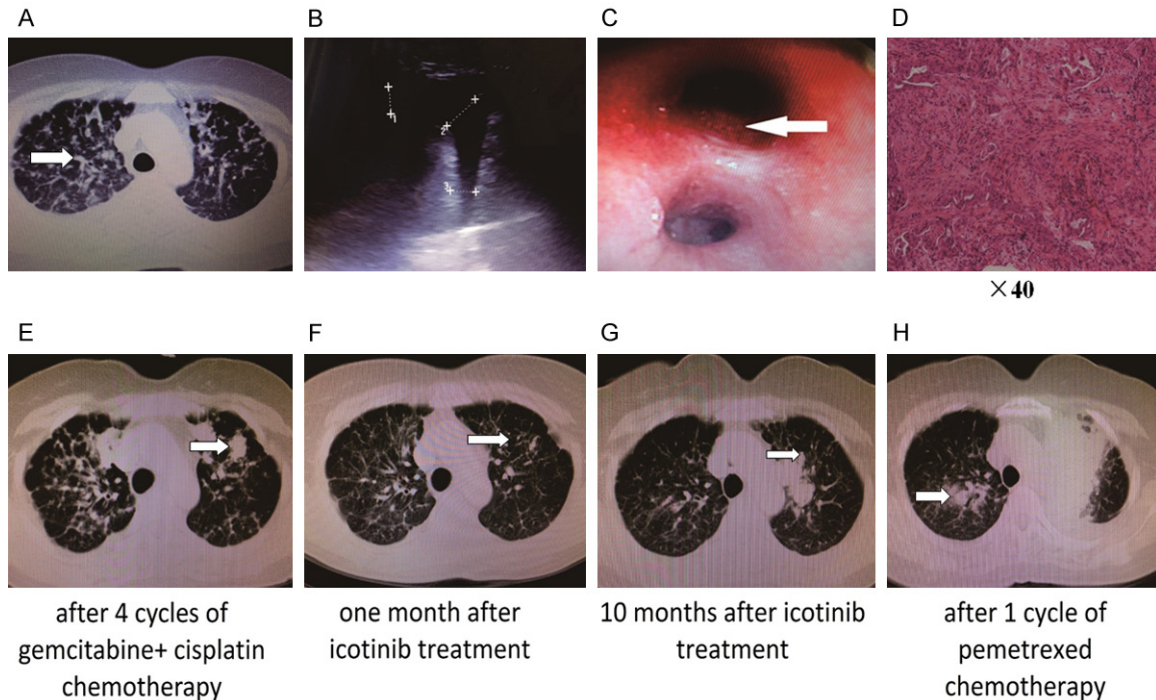
Epidermal growth factor receptor (EGFR) is one of the most important driver genes in patients with advanced non-small cell lung cancer (NSCLC). EGFR mutations have been confirmed to be strong predictive molecular markers for EGFR-TKI [1]. So EGFR-TKIs play very important roles in treatment of advanced EGFR mutated NSCLC, especially patients with lung adenocarcinoma harboring EGFR exon 19 or 21 mutations usually have dramatic responses to EGFR-TKI [2, 3]. However, acquired resistance to EGFR-TKI may develop inevitably and small cell lung cancer (SCLC) transformation is one of the acquired resistant mechanisms to EGFR-TKI [4, 5]. Here, we report one case of a histological transformation from adenocarcinoma to SCLC and then back to adenocarcinoma with EGFR exon 19 deletion after icotinib treatment. Also,

we review the relevant literature to clarify the molecular mechanisms, genetic characteristics and treatment strategies of SCLC transformation, and discuss whether SCLC can transform directly from adenocarcinoma or the SCLC component was initially combined with adenocarcinoma.

## Case presentation

A 58-year-old Chinese woman without smoking history presented to our department complaining of a 2 months cough in March 2014. Computed tomography (CT) revealed multiple bilateral nodules of the lung (**Figure 1A**). Then pericardial effusion was detected with cardiac ultrasound (**Figure 1B**) and congestion and swelling of the bronchial mucosa in the left upper lobe was showed by using bronchoscopy (**Figure 1C**). The patient then underwent broncho-

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**Figure 1.** Clinical, imaging and pathological findings at baseline before SCLC transformation. A. Chest CT scan showed multiple lesions in the lung. B. Echocardiography showed pericardial effusion. C. Image of the left main bronchus at the first bronchoscopy. The arrow indicates the site of biopsy. D. Hematoxylin-eosin (H&E) staining ( $\times 40$ ) of a bronchoscopic biopsy specimen confirmed adenocarcinoma. E. Chest CT scan after 4 cycles of gemcitabine plus cisplatin chemotherapy showed a disease progress. F. Chest CT scan showed a partial response one month after icotinib treatment. G. Chest CT scan showed disease progress 10 months after icotinib treatment. H. Chest CT scan showed a more aggressive disease after one cycle of pemetrexed. Key features in CT images are indicated by arrows.

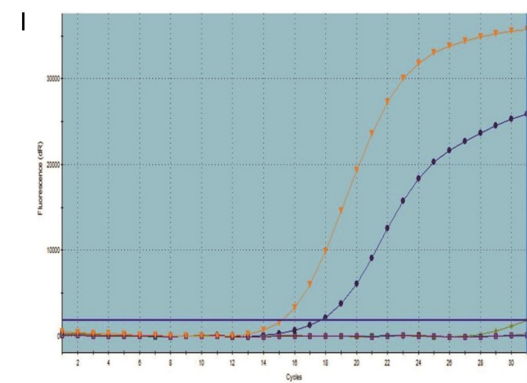
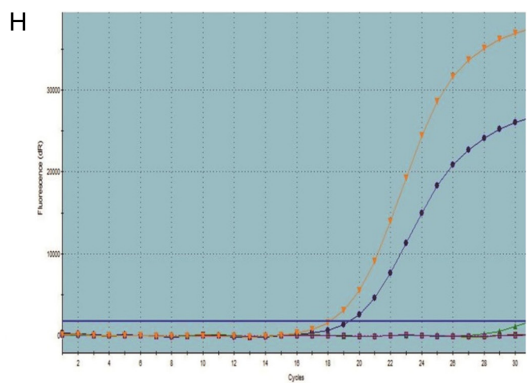
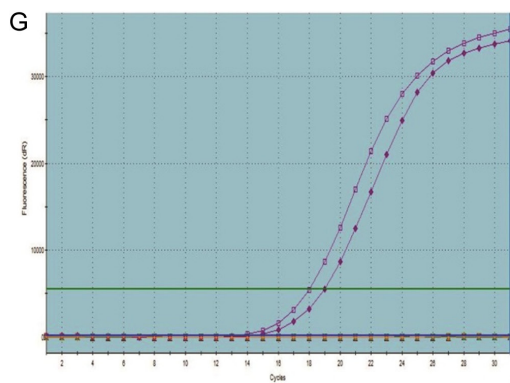
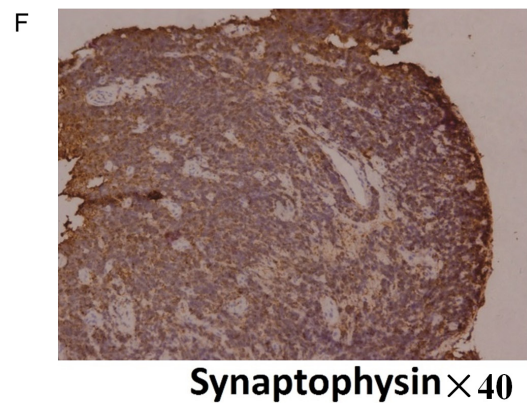
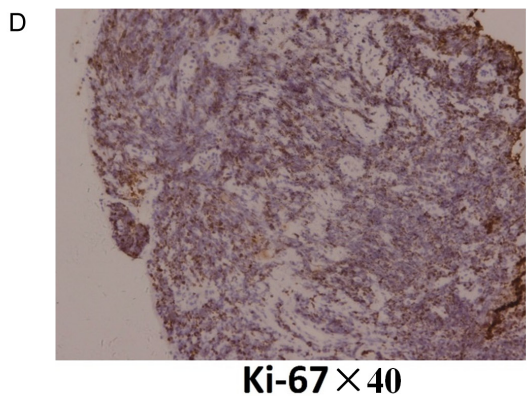
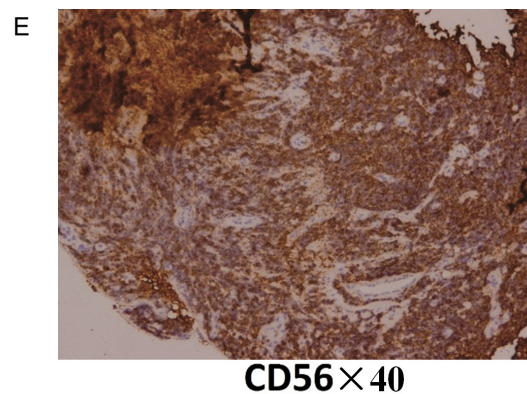
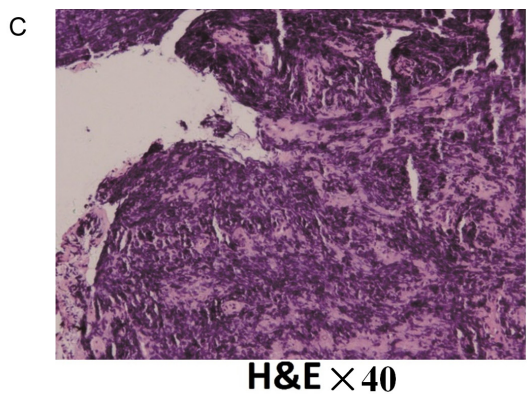
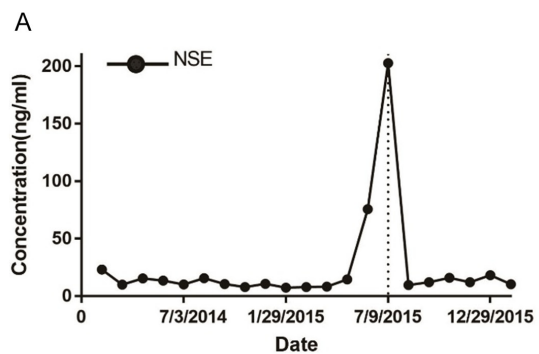
scopic biopsy, and the pathology result indicated pulmonary adenocarcinoma (**Figure 1D**). Also, this biopsy sample was genotyped and an EGFR exon 19 deletion (**Figure 2G**) was identified by using an amplification refractory mutation system (ARMS)-PCR method (AmoyDx Inc., Xiamen, P.R. China). She received first line chemotherapy with gemcitabine plus cisplatin and voluntarily participated in a randomized and controlled stage III clinical study. However, multiple nodules still not reduced in bilateral lung after finishing four cycles of chemotherapy (**Figure 1E**). So the female initiated treatment with icotinib (a new selective EGFR-TKI, which provides non-inferior efficacy to Gefitinib in NSCLC [6]) from August, 2014 and achieved partial response in one month (**Figure 1F**).

After that, the patient was followed up by using regular CT examination and the disease progress appeared after 10 months treatment of icotinib (**Figure 1G**). Given that drug resistance may happen, icotinib was discontinued. She

received one course of pemetrexed (500 mg/m<sup>2</sup> D1) as the third line therapy. What a pity was that the conditions were aggravated, and she began to feel chest tightness and shortness of breath. A chest CT scan showed a large mass at the left upper-lobe combined with obstructive pneumonia and pleural effusion (**Figure 1H**). The level of neuron-specific enolase (NSE) was elevated nearly nine-fold from 23.05 ng/ml at the baseline to 202.48 ng/ml (**Figure 2A**).

SCLC transformation was considered since the rapid progress of disease and the obvious up-regulation of NSE level were observed. The patient was suggested to take a second bronchoscopy. A visual neoplasm was observed at the beginning of the left upper-lobe (**Figure 2B**). Meanwhile, the biopsy was made through bronchoscopy and some sections of the neoplasm were subjected to additional H&E staining. The result indicated SCLC transformation might happen (**Figure 2C**). Further the immunohistochemical staining was done and results showed

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**Figure 2.** Clinical and pathological findings after SCLC transformation. (A) NSE serum level throughout the clinical course. The concentration of NSE elevated nearly nine folds when SCLC transformation occurred. (B) Bronchoscopic image of the left main bronchus after acquired resistance to icotinib developed. The arrow indicates the site of biopsy. (C) An H&E staining ( $\times 40$ ) of the biopsy showed SCLC transformation. Results of the immunohistochemical staining showed positive for Ki-67 (D), CD56 (E) and synaptophysin (F). Results of ARMS analyses showed the identical exon 19 deletion mutation of the first (G), second (H) and third biopsy (I).

positive staining with Ki-67 (**Figure 2D**), CD56 (**Figure 2E**) and synaptophysin (**Figure 2F**), which confirmed pathological diagnosis of SCLC. EGFR mutation test revealed exon 19 deletion again (**Figure 2H**)- the identical genotypic mutation but different pathological type from the former biopsy. She subsequently stopped using icotinib and underwent combination chemotherapy with etoposide plus carboplatin (EC) for two cycles. Then the patient felt uncomfortable symptoms relief significantly, chest CT scan manifested a partial response (**Figure 3A**) and the level of NSE reduced to 15.75 ng/ml (**Figure 2A**).

However, after four cycles of EC chemotherapy, some lesions at the left lobe became enlarged (**Figure 3B**) and an asymptomatic brain metastasis also emerged (**Figure 3D**). Thus the female was advised to take the third bronchoscopy, and swelling change of the mucosa was found in the left upper-lobe, but the neoplasm which had been seen before disappeared (**Figure 3F**). A bronchial mucosal biopsy specimen H&E staining, bronchial brush smear and sputum smear after bronchoscopy all demonstrated adenocarcinoma (**Figure 3G**). The exon 19 deletion of the EGFR gene was still detected from the biopsy specimen (**Figure 2I**) while the T790M mutation was negative. Due to the limitation of the sample size, c-MET and PI3KCA amplification have not been performed. Since there was no evidence of the EGFR T790M mutation, which elucidated the most popular mechanisms of acquired resistance to EGFR-TKI, icotinib was re-challenged combined with EC chemotherapy. After one month of oral icotinib administration and the fifth cycle of EC treatment, the lesions in the lung (**Figure 3C**) and in the brain were greatly improved (**Figure 3E**).

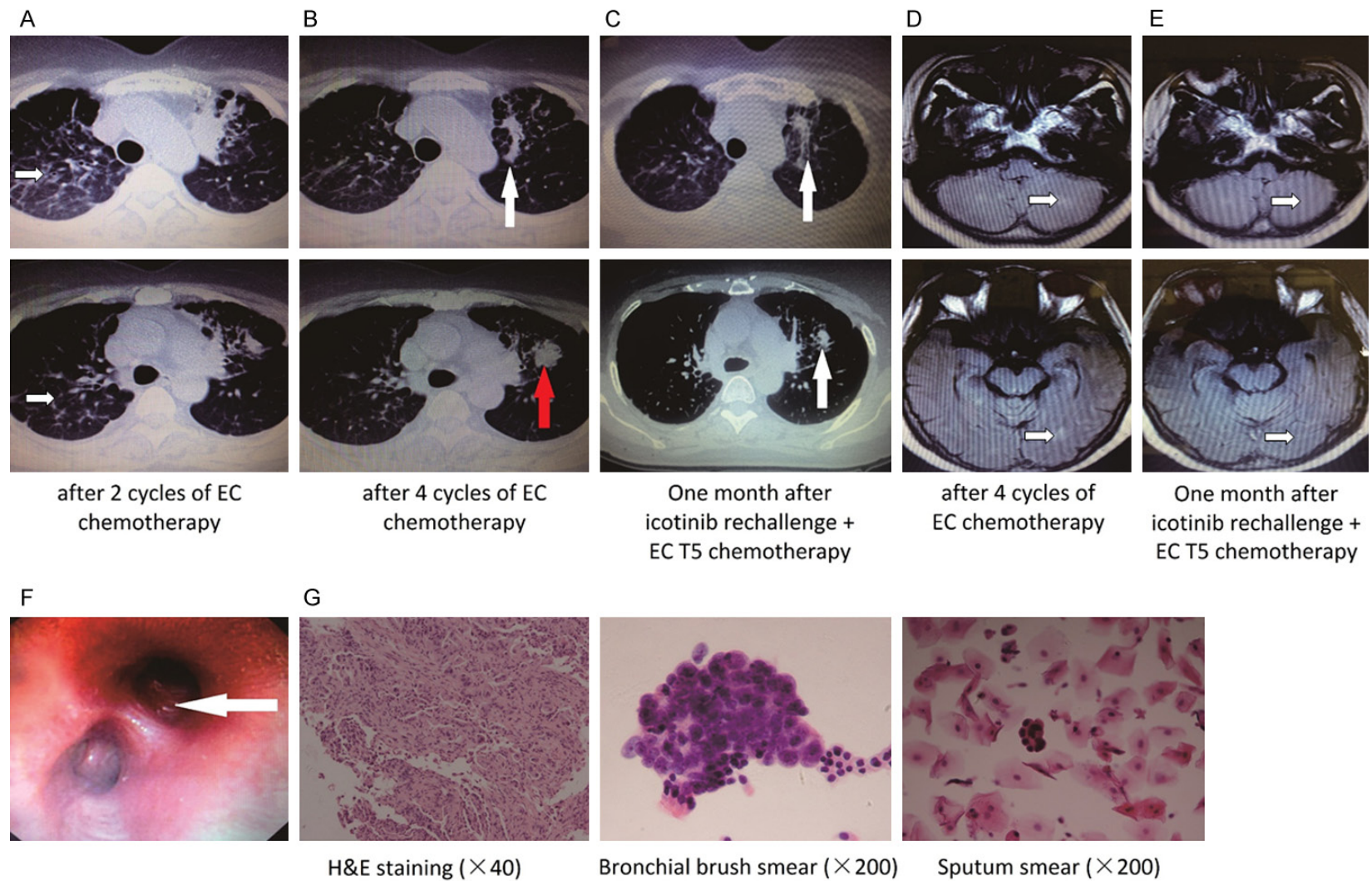
### Discussion

Icotinib, is a highly selective, new epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) which was developed in China. It is indicated for the treatment for EGFR mutation-

positive, advanced or metastatic NSCLC as a second-line or third-line treatment, for patients who have failed at least one prior treatment with platinum-based chemotherapy [6]. Part of mechanisms of acquired resistance to EGFR-TKI in advanced NSCLC have been revealed, including EGFR T790M mutation, MET amplification, PIK3CA mutation, BRAF mutation and SCLC transformation [7, 8].

Transformation to SCLC occurred to part of primary tumors was previously reported. An autopsy of a female patient with advanced NSCLC harboring EGFR exon 19 deletion treated with gefitinib for 15 months obtained nine metastatic lesions. These metastatic lesions consisted of six SCLCs, two adenocarcinomas and one retroperitoneum lymph node that contained both SCLC and adenocarcinoma components independently [9]. Another study [10] reported a case with progressed disease after the treatment of erlotinib whose supraclavicular lymph node biopsy showed SCLC transformation, but lung biopsy remained adenocarcinoma. Norkowski [11] also found two patients with lung adenocarcinoma had an occurrence of SCLC transformation in partial metastasis tumors after treated with EGFR-TKI. In most reported cases, biomarkers for SCLC including synaptophysin, CD56 and chromogranin were overexpressed [12-15]. What's more, in the cases previously reported, it might take 10 months to 3 years to get TKIs resistance and SCLC transformation [5, 13, 15]. In our case, the patient also took EGFR-TKI (icotinib) for 10 months until SCLC transformation discovered, which hinted the tumor transformation seemed to be driven by icotinib and this transformation is a course of transdifferentiation between SCLC and adenocarcinoma. Chang and his colleagues [16] found neuroendocrine differentiation from NSCLC cells could occur during acquisition of resistance to EGFR-TKI. In other studies [17], alveolar type II cells showed potential capability of differentiating to both adenocarcinoma and SCLC. When the EGFR signaling pathway was blocked by EGFR-TKI, the proliferation and dif-

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**Figure 3.** Clinical, Imaging and pathological findings before and after icotinib re-challenge. (A) Chest CT scan revealed a good response after 2 cycles of EC chemotherapy. (B) Some lesions were shrunken (white arrows indicate) after 4 cycles of EC chemotherapy, some lesions were enlarged (red arrows indicate). (C) The patient achieved a good response to icotinib combined EC chemotherapy. (D) Brain MRI showed new metastases developed after 4 cycles of EC chemotherapy, (E) which were improved after icotinib readministration. (F) Image of the third bronchoscopy showed infiltrative change in the left main bronchus. The arrow indicates the site of biopsy. (G) An H&E staining (×40) of the biopsy, a bronchial brush smear (×200) and a sputum smear (×200) revealed adenocarcinoma. Key features in CT and MRI images are indicated by arrows.

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differentiation of alveolar cells would be inhibited. If additional key genetic events occur, these alveolar type II cells may be transformed to SCLC and become independent of EGFR signaling. All these findings are positive evidence supporting the hypothesis of phenotype switching.

Nevertheless, previous studies also suggested the primary tumor may originally have a minor SCLC component [12, 13, 16, 18]. Samples obtained from bronchoscopy, fine-needle aspiration and pleural effusion may not provide sufficient material to detect the presence of combined histology at the diagnosis. After the adenocarcinoma was inhibited by EGFR-TKI, the SCLC component proliferated and could be detected easily. In our case, when the SCLC transformation was considered, the icotinib was discontinued and EC chemotherapy was given. Although the patient achieved a partial response after 2 cycles of EC, the disease still progressed after 4 EC cycles. So we do not think all adenocarcinoma cells can completely transform into SCLC cells at the same time. We consider the coexistence of adenocarcinoma and SCLC very likely happened at the same time of tumor development. The SCLC component may originate from adenocarcinoma cells or both cells were differentiated from a common cancer stem cell harboring the same EGFR mutation. Under TKI pressure selection, adenocarcinoma cells might be inhibited or eliminated, while SCLC cells proliferated. On the contrary, when the TKI stopped and EC started to use, the SCLC cells began to be killed but adenocarcinoma cells grew. Finally, the patient was greatly improved by administering icotinib combined with EC chemotherapy.

EGFR mutations in SCLC are rare, but transformed SCLC usually harbored the same type of mutation as the primary adenocarcinoma [12, 13, 18]. Furthermore, transformed SCLC cells showed lower expression of EGFR protein and lower level of EGFR amplification than parental adenocarcinoma cells [17]. Therefore, EGFR mutations may be considered as one of the main reasons about the SCLC transformation. Adenocarcinoma with sensitive EGFR mutations can transform into SCLC in the process of acquiring resistance to EGFR-TKIs [5]. In 2006, a female non-smoker SCLC patient was reported harboring EGFR gene 19 exon deletion [19]. In another two studies, the incidence of de novo SCLC patients with EGFR mu-

tation was 2.6% (2/76) and 1.6% (2/122) respectively [20], which were much lower than that in NSCLC. Interestingly, the frequency of EGFR mutation in SCLC transformed after EGFR-TKI treatment was significantly increased [21]. In most cases, the subtypes of EGFR mutation in SCLC transformed were the same as that in the primary tumor [5, 12, 22]. However, a case of NSCLC with EGFR gene 19 exon deletion transformed to SCLC with EGFR mutation in 21 exon E872K after EGFR-TKI treatment has been reported [11].

Analysis of re-biopsy samples from a patient underwent SCLC transformation after EGFR-TKI treatment revealed Rb1 mutation both in the lung and the liver metastasis, and this study also showed Rb loss in all nine lung adenocarcinomas with acquired resistance to EGFR-TKI that transformed to SCLC [17]. In another study, Rb1 mutation was found in the primary tumor but not in the SCLC transformed liver tumor [23]. Thus, Rb loss might be a necessary but not sufficient condition for SCLC transformation. Additionally, TP53 P151S mutations were also found both in the primary NSCLC tumor and the TKI-refractory lesions including liver metastasis samples with SCLC transformation [23]. Although PIK3CA is one of the driver genes in lung cancer with low mutation frequency [24], two cases of transformed small cell lung cancer with PIK3CA E545K had been reported [5, 17]. The accurate occurrence and the roles of driver gene alterations in SCLC transformed tumors warrants further investigation.

Currently, there are no predictive biomarkers that can preselect NSCLC patients who are more likely to develop SCLC transformation after EGFR-TKI treatment. In this case, the tumor progressed in spite of TKI treatment, accompanying with marked increase of the NSE level. The SCLC transformation was considered first and confirmed by followed repeat biopsies. Therefore, the rapidly increased NSE levels and tumor growth may point to SCLC transformation and support further biopsy, but large-scale studies should be required in the future. Re-biopsy is critical for histological diagnosis and molecular analysis. Also, there is no established worldwide guideline for the treatment of SCLC transformation. Some patients did benefit from classic chemotherapy (etoposide/irinotecan plus platinum) or radiotherapy [13, 24], but some patients received no res-



ponse [22]. All these suggested that the treatment strategies to conquer SCLC transformation should cover the SCLC transformed, combined NSCLC component and various EGFR-TKI acquired resistance mechanisms.

In summary, our findings not only underline the necessity of repeat biopsy after TKI resistance, but also highlight routine serum NSE test, as a non-invasive means, should be recommended for EGFR positive lung adenocarcinoma patients receiving EGFR-TKI treatments. Patients with SCLC transformation may still benefit from classic anti-SCLC therapies and effective comprehensive treatment for the combined NSCLC component.

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#### Disclosure of conflict of interest

None.

#### Abbreviations

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; EC, etoposide plus carboplatin; ARMS, amplification refractory mutation system; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer.

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