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# The clinicopathologic of pulmonary adenocarcinoma transformation to small cell lung cancer

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**Abstract**

Transformation to small cell lung cancer (SCLC) is one of the mechanisms of resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). However, it is uncertain how it works and there is no standard treatment after the transformation. In this study, 7 patients with transformation of SCLC from advanced lung adenocarcinoma (ADC) were analyzed retrospectively and the clinical pathology, imaging characteristics and treatment were analyzed.

We identified 7 patients with primary lung ADC that showed transformation to SCLC on second biopsy during a 6-year period. Clinicopathologic information was analyzed and EGFR mutation results were performed in initial biopsy samples.

Seven patients showed transformation from ADC to SCLC, of which 6 patients were 19 del EGFR mutation, only 1 patient is L858R mutations. The imaging forms did not have the typical imaging features of primary SCLC. All patients underwent etoposide and carboplatin (EC) regimen chemotherapy after pathological transformation. However, the response rate of EC was less than primary small cell lung cancer. One of the patients was receiving EC for 4 cycles. After chemotherapy the patients performed radiation therapy and finally with erlotinib maintains treatment, the progress free survival (PFS) was more than 12 months.

NSCLC can acquire a neuroendocrine phenotype with EGFR-TKI treatment. The transmutation is more common in 19del mutation patients. A comprehensive treatment based on EC regimen chemotherapy and the maintenance with EGFR-TKI is likely to be the appropriate treatment for these patients.

**Abbreviations:** ADC = adenocarcinoma, ASCL1 = achaete-scute homolog 1, CDK5 = cyclin-dependent kinase 5, CT = computed tomography scan, EC = etoposide and carboplatin, EGFR = epidermal growth factor receptor, NSCLC = non-small-cell lung cancer, PFS = progress free survival, SCLC = small cell lung cancer, TKIs = tyrosine kinase inhibitors.

**Keywords:** lung adenocarcinoma, resistance to EGFR-TKI, SCLC

## 1. Introduction

Lung cancer is classified into 2 histological subgroups: nonsmall cell lung cancer (NSCLC) and small cell lung cancer (SCLC). The distinction between these 2 categories is important because the treatment options differently. The chemotherapeutic regimens for SCLC and NSCLC are different.[1,2] Currently, the first-line treatment for a subset of EGFR-mutated NSCLC patients is epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs).[3] In many cases, secondary T790M mutation has been well-described and reported in up to 60% of resistant samples,[4] there have been several studies proposing histological transformation from NSCLC to SCLC as another mechanism of

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EGFR-TKI resistance.[2,4] The possible explanation of this phenomenon can be the transformation of NSCLC, mostly ADC, to high-grade neuroendocrine phenotype.[2] The reports showed that every transformed SCLC tumor sample retained its original EGFR-activating mutation,[5,6] supporting the idea that these were not independent second-primary cancers.[2] In addition, many patients with transformed SCLC tumors were female nonsmokers,[5,6] which is different from the typical SCLC patient demographic.

During active treatment with targeted therapies, there are 3% to 15% of patients transformation to SCLC in NSCLC tumors. By definition, SCLC is a high-grade tumor with genetic characteristics and specific histological. However, the recent reports of transformation from NSCLC to SCLC evoke some questions regarding the origin of SCLC. It is not certain whether transformation to SCLC is exclusively found as a mechanism of EGFR-TKI resistance tumors. Practical questions include whether re-biopsy is indicated after EGFR-TKI resistance develops following treatment initiation, especially since a good response after switching to a SCLC chemotherapy regimen in transformed SCLC tumors has been reported.[7] The molecular mechanisms that drive the histopathological transformation to SCLC in NSCLC tumors is still unknown. It is needed further investigation.

Here, we report 7 cases of SCLC transformed from pulmonary ADC in a single institute during a 5-year period.

## 2. Material and methods

### 2.1. Patients

During a 6-year period (2012–2018), there were a total of 7 ADC in our institute transformed to SCLC morphology in second biopsy. The ADC was originated from the bronchial mucosal epithelium and the pathological diagnostic criteria of ADC was TTF-1(+), Napsin-A(+), p63(−), p40(−). The pathological diagnostic criteria of SCLC was CD56(+), Syn(+), and Cga(+). Three experienced pathologists reviewed the histological slides. All patients were treated in the Department of Lung Cancer and Gastroenterology, Hunan caner hospital (Changsha, China). Clinical and follow-up data were obtained through a retrospective analysis, including age, sex, smoking history, clinical stage, and treatment. The study was approved by the Hunan Caner Hospital.

### 2.2. EGFR mutation test

DNA was profiled by using a capture-based targeted sequencing panel (Burning Rock Biotech, Guangzhou, People's Republic of China), including all exons in several genes. Qubit dsDNA was used to assay the concentration of the DNA samples. Fragments of 200 to 400-bp sizes were selected with beads (Agencourt AMPure XP kit; Beckman-Coulter, Brea, CA), followed by hybridization with the capture probes baits, hybrid selection with magnetic beads, and PCR amplification. A bioanalyzer high-sensitivity DNA assay was then used to assess the quality and size range. Available indexed samples were then sequenced on a Nextseq (Illumina, San Diego, CA) with pair end reads. Sequence data were analyzed by GATK 3.2 (https://www.broadinstitute.org/gatk/) and DNA translocation analysis was performed by using both Tophat2 (http://ccb.jhu.edu/software/tophat/index.shtml) and Factera 1.4.3 (http://factera. stanford.edu).

### 2.3. Hematoxylin and eosin (H&E) staining

Lungs were fixed in 4% formaldehyde, and 5 μm sections were stained with hematoxylin and eosin (HE) reagent and examined with a Nikon microscope (×20 magnification). The specific protocol was according to the kit instruction (Thermo Fisher).

### 2.4. Immunohistochemistry

The tissue staining was fixed in 4% paraformaldehyde and embedded in paraffin. Three micrometer thick sections were prepared, and immunohistochemical staining of CD56 (123C3, dilution 1:200, Cell Signaling Technology, Danvers, MA), TTF-1 (dilution D2E8,1:150, Cell Signaling Technology, Danvers, MA) were performed using a DAKO Autostainer Plus system. Each section was examined under a ×200 power field in a double-blinded manner.

## 3. Results

### 3.1. Patients information

Seven patients showed NSCLC transformed to SCLC with 3 females and 4 males. Patients information and pathologic features were summarized in Table 1. The mean age was 53 years old. Three in 7 patients were smoking for more than 10 years. All the initial samples with diagnosis of ADC, 6 of the cases were obtained using needle biopsy and one was surgically resected specimens. The second biopsies were obtained using lung puncture biopsy and lymph node biopsy. All samples that showed transformation to SCLC upon second biopsy, 7 showed pure SCLC morphology. For small cell components, CD56 was expressed in all available cases. CD56 was not expressed in ADC components (Fig. 1).

**Table 1**

**Patients information and pathologic features of 6 patients showing transformation from non-small-cell lung cancer to small cell lung cancer.**

| Case no | Age | Sex, years | Smoking history, years | Initial tumor | Sample type | Transformed tumor | Sample type | IHC TTF-1/CD56 |
|---|---|---|---|---|---|---|---|---|
| 1 | F | 53 | None | ADC | Needle biopsy | SCLC | Lung puncture biopsy | +/+ |
| 2 | F | 63 | None | ADC | Needle biopsy | SCLC | Lymph node biopsy | −/+ |
| 3 | M | 48 | None | ADC | Resected | SCLC | Lung puncture biopsy | +/+ |
| 4 | M | 42 | 10 | ADC | Needle biopsy | SCLC | Lung puncture biopsy | +/+ |
| 5 | F | 48 | 24 | ADC | Needle biopsy | SCLC | Lung puncture biopsy | +/+ |
| 6 | M | 58 | 20 | ADC | Needle biopsy | SCLC | Lung puncture biopsy | +/+ |
| 7 | M | 60 | None | ADC | Needle biopsy | SCLC | Lymph node biopsy | +/+ |

ADC = adenocarcinoma, F = female, IHC = immunohistochemistry, LN = lymph node, M = male, NA = not-applicable. [a]CD56 was positive in only SCLC components, SCLC = small cell lung cancer, TTF-1 = thyroid transcription factor.

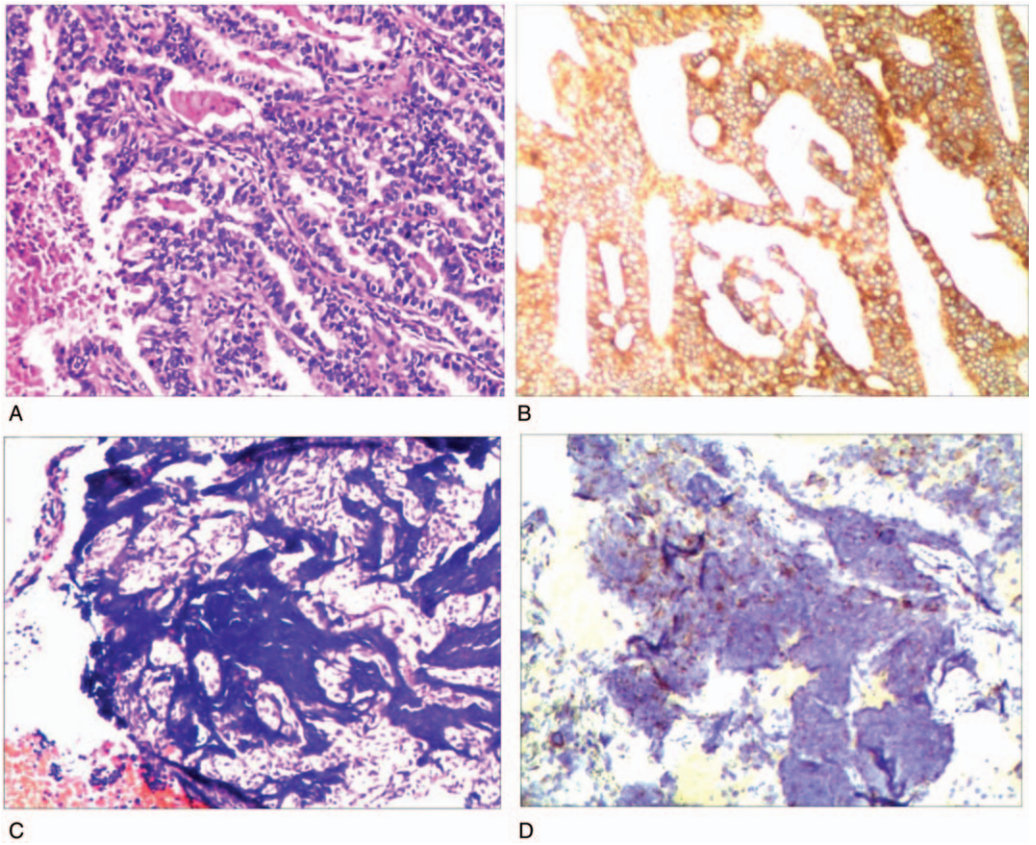


**Figure 1.** Case 3 showing transformation to small cell lung cancer. (A) Initial biopsy of case 3. Hematoxylin and eosin (H&E) showed differentiated adenocarcinoma (×200). (B) Positive immunohistochemistry (IHC) for TTF-1 (×200). (C) After transformation tumor cells, H&E stain showed tumor composed of nests of small cells with fine granular chromatin nuclei, and scarce cytoplasm (×200). (D) Positive IHC for CD56 (×200).

### *3.2. Clinical information and treatment*

The clinical information including EGFR mutation status and therapy were summarized in Table 2. All of the patients TNM stage were IV. Of the 7 patients with ADC in initial biopsy, they harbored an EGFR mutation (L858R mutation, n = 1; exon 19 deletion, n = 6). Cases 1 and 3, 5, 6, 7 were treated with erlotinib, and gefetinib was giving for case 2 and 4. All of the patients acquired secondary biopsy after progress received EGFR-TKI treatment. After confirmation of transformation to SCLC on second biopsy, all of the patients received secondary genetic testing. The gene test showed that case 1, 3, 5, and 6 with EGFR mutation (case 1, 3 and 5 with exon 19 deletion; case 6 with T790M mutant). The patients received further treatment. The treatment option for 7 patients was switched to etoposide and cisplatin (EC) with or without EGFR-TKI. It is interesting to us that case 3 was receiving EC for 4 cycles. After chemotherapy the patients performed radiation therapy and finally with erlotinib maintains treatment, the PFS was more than 12 months. The other cases were <7 months. Case 4, 5, 7 died due to disease progression and the other patients were alive in the short-term

**Table 2**

**Clinical information and *EGFR* status of 7 patients showing transformation from non-small-cell lung cancer to small cell lung cancer.**

| Case no | Initial tumor | Clinical stage | EGFR mutation | Treatment with TKI | Response to TKI, months | Transformed tumor | Secondary genetic testing | Treatment after transformation | PFS to secondary treatment, months | PFS to secondary treatment, months | Death |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | ADC | IV | 19del | Erlotinib | PD (13m) | SCLC | 19del | EC + erlotinib | PD (3m) | | |
| 2 | ADC | IV | 19del | Gefetinib | PD (17m) | SCLC | No mutant | EC | PD (2m) | SD (3m) | Alive |
| 3 | ADC | IV | 19del | Erlotinib | PD (22m) | SCLC | 19del | EC + radiation + Erlotinib maintenance | SD (12m) | SD (2m) | Alive |
| 4 | ADC | IV | L858R | Gefetinib | PD (29m) | SCLC | No mutant | EC | PD (2m) | SD (12m) | Alive |
| 5 | ADC | IV | 19del | Erlotinib | PD (16m) | SCLC | 19del | EC insert erlotinib + Erlotinib maintenance | PD (7m) | SD (2m) | Death |
| 6 | ADC | IV | 19del | Erlotinib | PD (24m) | SCLC | T790M | EC + osimertinib | PD (4m) | SD (7m) | Death |
| 7 | ADC | IV | 19del | Erlotinib | PD (14m) | SCLC | No mutant | EC | PD (1m) | SD (4m) | Alive |

ADC = adenocarcinoma, EC = etoposide and cisplatin, EGFR = epidermal growth factor receptor, PD = progressive disease, SCLC = small cell lung cancer, SD = stable disease, TKI = tyrosine kinase inhibitor.

follow-up period. Meanwhile, computed tomography (CT) scan enhancement was used to evaluate the efficacy of 7 patients at the initial diagnosis, efficacy evaluation and after transformation to SCLC. The CT manifestation were different from the typical primary small cell lung cancer that showed increasing the primary tumor, double lung nodules, pleural nodules, and pleural effusion and isolation nodules.

### 3.3. Typical case

It is well known that after transformation to SCLC, it is difficult to choose the best treatment due to there is no consensus on the treatment option and acquired poorly PFS. However, it is fantastic that case 3 received EC combine radiation therapy and finally with erlotinib maintains treatment, the progress free survival (PFS) was more than 12 months. Case 3 was a 48-year-old man with no history of smoking was admitted to our hospital with exacerbation of cough. CT of the chest revealed a right lower lobe lung tumor and right middle lung nodules (Fig. 2). Bronchoscopic biopsy of the tumor revealed negative result. Hence the right lower lung mass removal and right middle lung nodules biopsy were performed. The pathology showed right middle lung and right lower lung were differentiated adenocarcinoma (Fig. 1). The gene test demonstrates EGFR gene mutation (exon 19 deletion) as shown in Figure 3. For the next years, he was treated with erlotinib, an EGFR-TKI and CT evaluated as partial response (PR) (Fig. 2). After 22 months with erlotinib, disease progression was again noted through CT scan which showed soft tissue density mass in the right hilum of the lung (Fig. 2). We once again performed bronchoscopic biopsy of the tumor, and SCLC was confirmed from histopathological examination (Fig. 1). Moreover, a second examination again detected the EGFR gene mutation (exon 19 deletion without T790M point mutation) (Fig. 3). The patient was receiving EC for 4 cycles. After chemotherapy the patients performed radiation therapy and finally with erlotinib maintain treatment, the PFS was more than 12 months. CT re-examination showed that the condition was stable diseased (SD) (Fig. 2). Case 5 also translated to SCLC and received EC for 4 cycles and insert with erlotinib. Once the chemotherapy was finished the patients performed erlotinib maintains and the PFS was 7 months. The specific clinical data were shown in supplementary, http://links.lww.com/MD/C886.

## 4. Discussion

It is reported that 50% to 60% of patients who develop resistance to EGFR-TKI with T790M mutation and received third generation EGFR-TKI, which is reported in current targeted therapies.[8] Other mechanisms such as MET and HER2 amplification, make up 15% to 20% of acquired resistance to EGFR-targeted therapies.[9–11] More and more study had reported that transformation of NSCLC to SCLC maybe an underlying mechanism of resistance to TKI therapy that occupy 3% to 15% of patients.[2,5] Once the patients transform to SCLC, the treatment plan will change. However, most reports of transformation of ADC to SCLC were identified in EGFR mutant patients related to TKI treatment, the underlying mechanism is still unclear.[12] Here, we report 7 cases of ADC which showed histologic transformation to SCLC with pathological evidence.

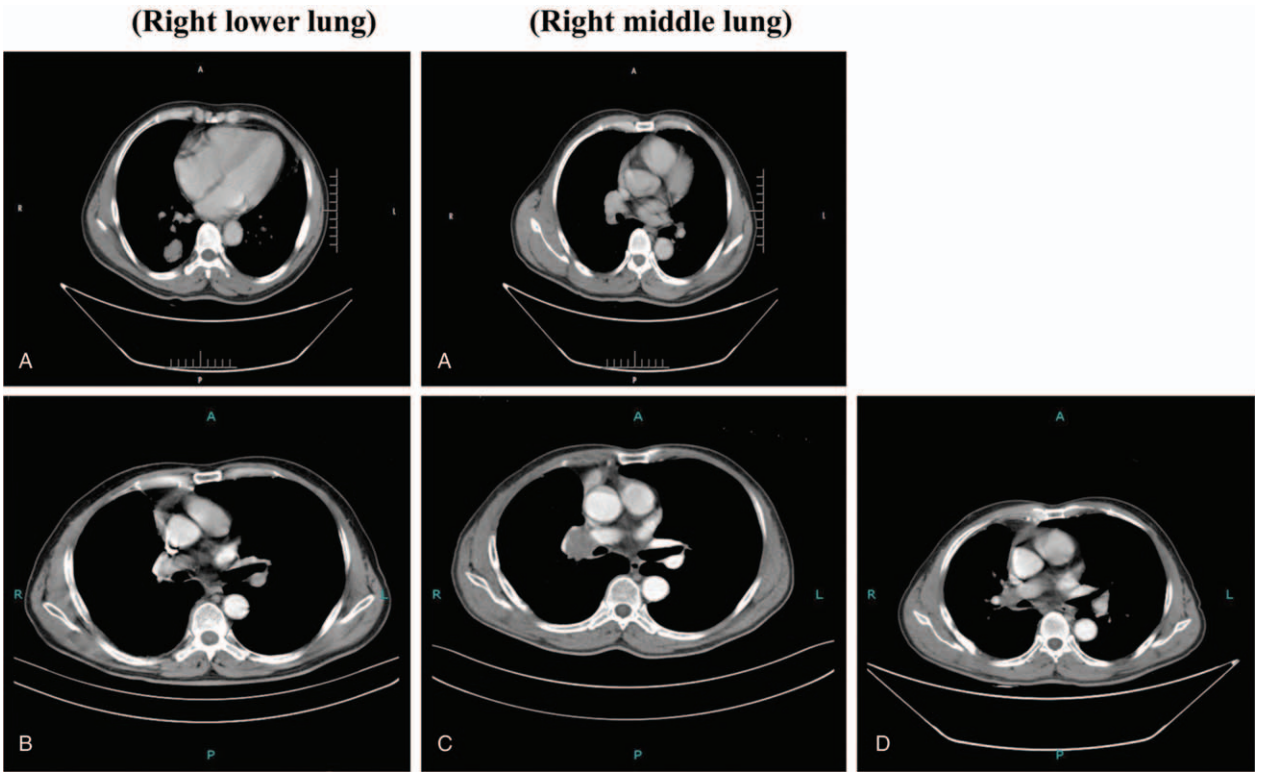


**Figure 2.** Chest computed tomographyscan finding. (A) The initial CT revealed a right lower lobe lung tumor and right middle lung nodules. (B) During the erlotinib treatment, CT evaluated as partial response (PR); (C) After 22 months with erlotinib, disease progression noted through CT scan which showed soft tissue density mass in the right hilum of the lung. (D) After transformation, the patient was receiving EC for 4 cycles and following radiation therapy and finally with erlotinib maintains treatment. CT re-examination showed that the condition was stable diseased (SD).

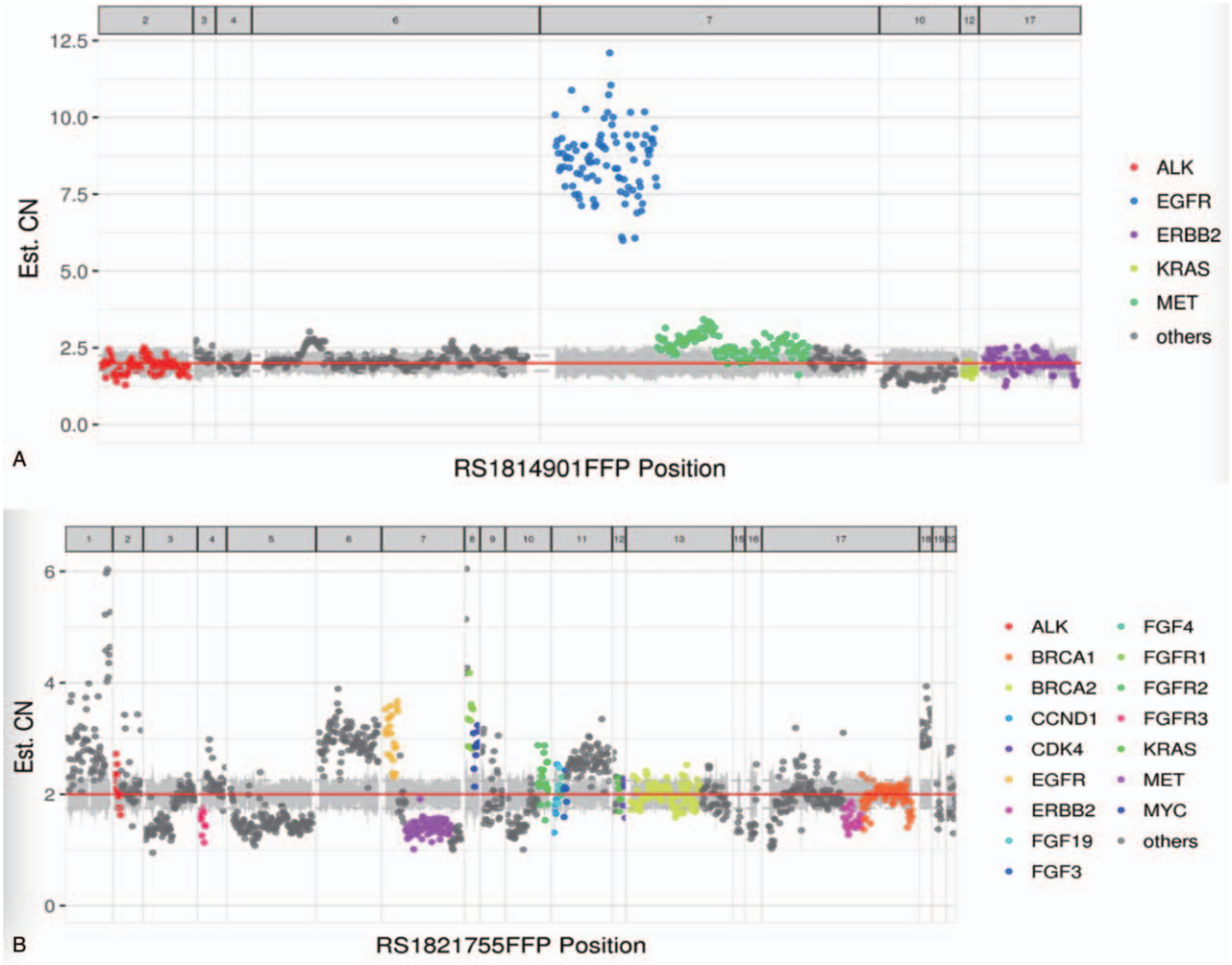


**Figure 3.** Gene testing finding. (A) The initial gene test demonstrates EGFR gene mutation (exon 19 deletion). The mutant abundance was 68.3%. (B) A second examination again detected the EGFR gene mutation (exon 19 deletion without T790M point mutation). The mutant abundance was 66.34%. EGFR = epidermal growth factor receptor.

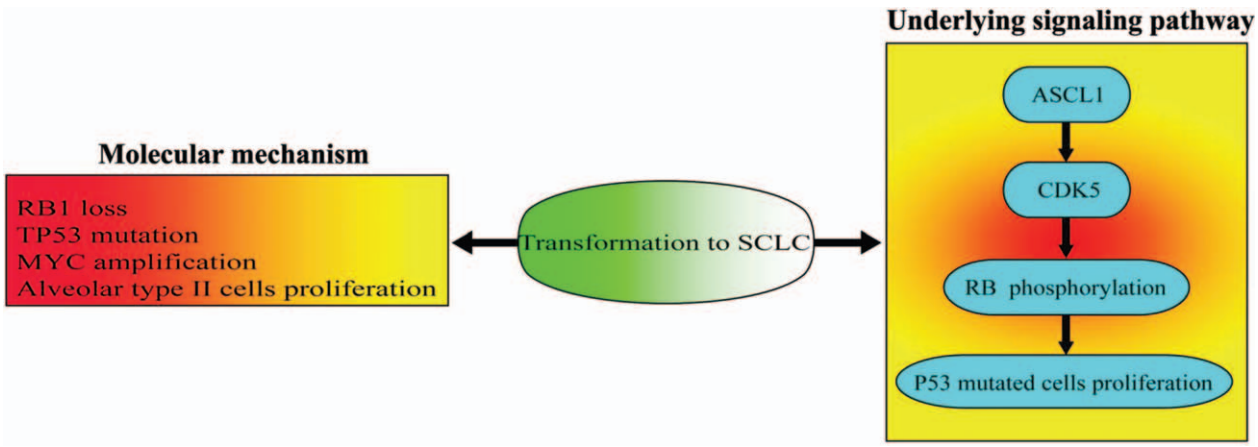


**Figure 4.** The mechanisms involved in the transformation from NSCLC to SCLC. They include RB1 loss, TP53 mutations, MYC amplification and alvelor type II cells proliferation. The most underlying signaling pathway is the ASCL1 target CDK5 activity and inactivation of RB by phosphorylation. With inactivated RB, p53 mutated cells have a selective advantage. ASCL1 = achaete-scute homolog 1, CDK5 = cyclin-dependent kinase 5, RB1 = retinoblastoma 1, SCLC = small cell lung carcinoma.

All of cases in our series were ADC with EGFR activating mutations that underwent TKI treatment and were subsequently found to have SCLC transformation on re-biopsy.

Before the discovery of the EGFR activating mutations, when some patients received conventional chemotherapy or radiotherapy and acquired resistance, almost 5% of patients transformed from NSCLC to SCLC. Although it is unknown whether these patients had any EGFR-activating mutations, but they showed SCLC transformation independent of EGFR inhibition.[13] At present EGFR-mutated adenocarcinomas are more common and almost 3% to 15% of patients underwent transformation to SCLC. However, the underlying molecular mechanism involved in the transformation from NSCLC to SCLC is still unknown. Two SCLC genome-sequencing projects have been finished that could analysis of the transcriptome, genome, and the copy number. The 2 fantastic projects identified a high prevalence of TP53 and RB1 mutations.[14,15] The MYC amplification was observed in 16% of the studied cases.[14] The role of proliferation in cells of SCLC will diminished once MYCL1 knockdown,[15] which indicating that MYC can function as an oncogenic marker in a subgroup of SCLC tumors. The loss of RB1 is more common in SCLC.[16] The patients resistant to EGFR-TKI was performed re-biopsies that underwent SCLC transformation have shown that all the tumors had lost RB1. On the other way, it is found that achaete-scute homolog 1 (ASCL1) promotes more aggressive adenocarcinoma growth and may interact with the central retinoblastoma protein-tumor protein 53 (RB-p53) axis and caused inactication of RB by phosphorylation in the carcinogenesis of neuroendocrine lung cancers. The RB phosphorylation is triggered by targeting cyclin-dependent kinase 5 (CDK5) (Fig. 4).[17,18]

In our study all of patients with EGFR mutant type ADC who developed second biopsy showed transformation NSCLC to SCLC, especially with EGFR 19del deletion. However, it does not mean that transformation to SCLC in the unique to tumor-bearing EGFR mutations. A study reported that EGFR wild-type ADC with TKI resistance also bearing SCLC transformation.[19] However, the problem was that the incidence of transformation of NSCLC to SCLC not always accurately calculated. An acquired TKI resistance arising from the histological transformation to SCLC has been reported to be as high as 3% to 15%.[2,5] In contrast, the incidence of transformation of NSCLC to SCLC identified in our institution by secondary biopsy was 1.7% due to loss some of patients in EGFR mutant ADC during treatment with AZD9291, an oral irreversible EGFR-TKI with selectivity for activating EGFR mutations and the T790M resistance mutation. The patients with EGFR mutant ADC who were resistant to AZD9291 therapy maybe also transformed from NSCLC to SCLC. The other problem that once transformation to the SCLC is that the treatment option is not uniform and the mechanism is still unclear. In our cases, all the patients were received second biopsy and performed gene test to find the underling transformed mechanism. Unfortunately, we have not find the mechanism. Hence, it is imperative for us that find the transformed mechanism in the future.

It is well known that the classic treatment for SCLC is EC. Four cases had persistent existing EGFR mutations who received continue TKI treatment. It is amazing to us that one of the cases acquired 12 months PFS. However, we lack clinical trials that address the best way to treat SCLC transformed from NSCLC tumors. Case reports and series of cases in the literature, used standard chemotherapy (EC) and reported a response in 70% of the patients.[5,6] It is pity for us that we cannot clarify the difference of response rate, overall survival of EC chemotherapy and EGFT-TKI therapy between this population and other lung cancer because of lacking of the numbers of clinical studies. Hence, it is imperative for us to perform clinical studied to prove the best treatment for ADC transformation into SCLC.

## 5. Conclusion

Taken together, we report 7 cases transformation from ADC to SCLC of which 6 patients were 19 del EGFR mutation, only 1 patient is L858R mutations. All patients underwent EC regimen chemotherapy after pathological transformation. One of the patients was receiving EC for 4 cycles. After chemotherapy, the patients performed radiation therapy and finally with erlotinib maintains and acquired longer PFS compared to the purely chemotherapy. It is indicated that chemotherapy combined with TKI may be an ideal treatment model for advanced lung adenocarcinoma with EGFR sensitive mutation who transformation into SCLC.

## Author contributions

Jingjing Qu performed experiment. Haiyan Yang, Chunhua Zhou, and Li Liu provide the information of patients, Yijuan Hu collection of data, Jingjing Qu, Haiyan Yang, and Nong Yang conception and design, financial support, manuscript writing, and final approval of manuscript.
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**Formal analysis:** Chunhua Zhou, Nong Yang.
**Funding acquisition:** Jingjing Qu.
**Investigation:** Haiyan Yang, Li Liu, Nong Yang.
**Methodology:** Jingjing Qu, Chunhua Zhou, Yijuan Hu.
**Resources:** Haiyan Yang.
**Writing – original draft:** Jingjing Qu.

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