Original Article

Clinicopathological features of patients with transformation from *EGFR* mutant lung adenocarcinoma to small cell lung cancer

Wenwen Bai^, Chanjun Zhen, Ruohui Zhang, Wenhui Yu, Zhiguo Zhou^

Department of Radiation Oncology, the Fourth Hospital of Hebei Medical University, Shijiazhuang, China

Contributions: (I) Conception and design: Z Zhou, W Bai; (II) Administrative support: Z Zhou; (III) Provision of study materials or patients: W Bai, Z Zhou, C Zhen; (IV) Collection and assembly of data: W Bai, R Zhang, W Yu; (V) Data analysis and interpretation: W Bai, C Zhen, Z Zhou; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Zhiguo Zhou. Department of Radiation Oncology, the Fourth Hospital of Hebei Medical University, No. 12 Jiankang Road, Shijiazhuang 0500l1, China. Email: chenk777@126.com.

Background: Recently, an increasing number of cases with transformation from lung adenocarcinoma to small cell lung cancer (SCLC) have been identified, but few studies have investigated the clinical, pathological as well as molecular characteristics of these cases. This study aimed to summarize and analyze these features.

Methods: We retrospectively collected data including clinical information, laboratory examination results, radiological and pathological findings of ten patients, who were confirmed to undergo SCLC transformation following treatment from January 2014 to January 2020.

Results: The median time of treatment (targeted agents) was 14 months, and the median time interval of SCLC transformation following treatment was 24 months. Immunohistochemical indicators after transformation showed positive thyroid transcription factor 1 (TTF1), synaptophysin (Syn), CD56, and AE1/AE3, highly expressed Ki67, as well as negative programmed cell death-ligand 1 (PD-L1). Compared with the patients who received targeted therapy first, those patients who received chemotherapy followed by targeted therapy presented longer time intervals to transformation (36 *vs.* 22 months). Genetic testing after transformation showed that eight patients still maintained the original epidermal growth factor receptor (*EGFR*) mutation types. The median progression-free survival (PFS) after transformation was 5 months, and the median survival time after transformation was 10 months in seven patients who died.

Conclusions: Lung adenocarcinomas, once transformed to SCLC, progress rapidly and lead to poorer prognosis. After transformation, most of the patients maintain the original *EGFR* mutation types.

Keywords: Lung cancer; adenocarcinoma; small cell carcinoma; transformation; prognosis

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Introduction

Currently, lung cancer is the most common cancer in the world, demonstrating the highest morbidity and mortality (1). Among them, non-small cell lung cancer (NSCLC) accounts for 80–85% of the total cases. Adenocarcinoma accounts for more than half of cases in terms of histological type. With the rapid development of precision medicine, molecular targeted drugs, such as epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), have achieved encouraging outcomes in patients with advanced NSCLC. However, most patients inevitably developed acquired resistance

^ ORCID: Wenwen Bai, 0000-0002-7037-648X; Zhiguo Zhou, 0000-0002-5373-8098.

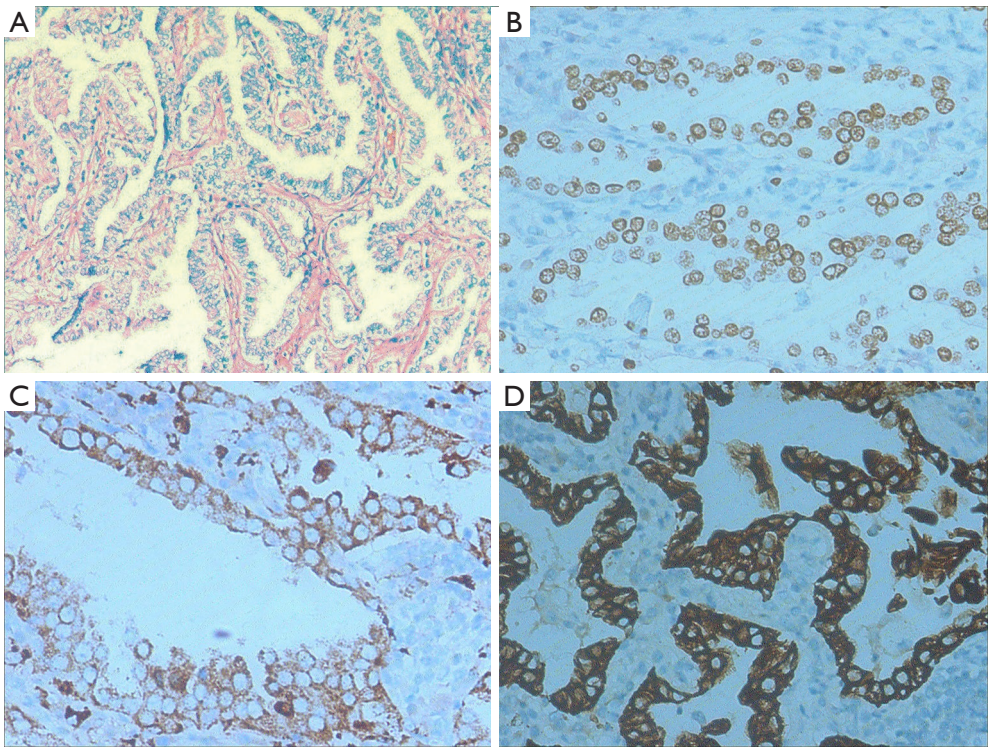

Figure 1 Pathological and immunohistochemical examination of case 1 at initial diagnosis (adenocarcinoma). (A) The initial pathology (H&E, ×10). (B) TTF-1 positive (IHC, ×20). (C) Napsin A positive (IHC, ×20). (D) CK positive (IHC, ×20). H&E, hematoxylin-eosin staining; IHC, immunohistochemical staining; TTF-1, thyroid transcription factor 1; CK, cytokeratin.

at 10–12 months after treatment (2). At present, the most common resistance mechanism is the T790M mutation, accounting for approximately 60%. Other causes of resistance include c-Met gene amplification, human epidermal growth factor receptor 2 (HER2) gene amplification and the transformation of small cell lung cancer (SCLC) (3). Among them, the transformation of NSCLC to SCLC has brought much confusion to clinical diagnosis and treatment. Therefore, we should not ignore this unique phenomenon because of the low incidence. In 2006, Zakowski *et al.* first reported a NSCLC patient who was diagnosed with SCLC accompanied by the *EGFR* exon 19 mutation after TKI treatment (4). However, this patient had not undergone *EGFR* genetic test before the treatment. Subsequently, an increasing number of cases have been reported to exhibit such phenomenon (5-7), but few retrospective studies are currently able to analyze these cases meticulously and comprehensively. This study aimed to summarize and analyze the clinicopathological features of the patients with the transformation from lung adenocarcinoma into SCLC, thus providing a reference for future practice in clinic.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/tcr-21-653).

Methods

Case data

We collected the clinical and pathological data of ten patients who developed the transformation from lung adenocarcinoma to SCLC (mixed pathological types were excluded) following treatment from January 2014 to January 2020 in the Fourth Hospital of Hebei Medical University. Among them, seven cases were males and three were females. The average age was 55 (ranged from 30 to 68) years. All the patients were initially diagnosed with adenocarcinoma based on the pathological examination. However, only two cases underwent immunohistochemical examination (the pathological and immunohistochemical findings of case 1 at the first

diagnosis were shown on *Figure 1*). Before transformation, three patients underwent resection of lower lobe of left lung with postoperative pathological examination, whereas the remaining seven patients underwent biopsies of lung masses. While all patients underwent needle biopsies and immunohistochemical examination to confirm the pathological diagnosis of SCLC after transformation. The neuron-specific enolase (NSE) values were 12.03, 14.76, 23.42, 15.26, 12.34, 10.51, 14.29, 11.83, 11.83, 12.62 μg/L (reference value range: 0–16.3 ng/L) in the included patients, and slightly elevated in one patient. The remaining information is summarized in *Table 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee board of the Fourth Hospital of Hebei Medical University (2020KY254) and individual consent for this retrospective analysis was waived.

Study design

We collected data including clinical information, laboratory examination results, radiological and pathological findings among the ten patients. Specifically, a retrospective review of the patients' medical records was performed focusing on the levels of tumor markers before transformation, the time point of SCLC transformation, gene mutation status before and after transformation, as well as the progression-free survival (PFS) and overall survival (OS) after transformation. The specific treatment for the 10 patients before transformation is displayed in *Table 2*. Genotyping was performed with next-generation sequencing (NGS). Besides, the pathological diagnosis was made by routine histopathological sections, which were stained with a Vantana automatic immunohistochemical staining instrument. The proportion of cells with positive programmed cell death-ligand 1 (PD-L1) expression was obtained by DAKO 22C3 pharmDx and VENTANA SP263.

Follow-up

The cutoff date for follow-up was August 1, 2020.

Statistical analysis

Statistical analysis was performed using SPSS 22.0 software. Descriptive statistics were presented as mean (or median) and range.

Results

Clinical characteristics

EGFR gene mutations were detected before the initial diagnosis in 9 of 10 patients, including 8 patients with *EGFR* exon 19 del (*EGFR* E19) mutation and 1 patient with *EGFR* exon 21 del L858R (*EGFR* E21 L858R) mutation based on their blood specimens. A caveat to this is that no gene mutation was found in case 10 at the initial diagnosis, therefore, TKI therapy was not provided. The median time of TKI treatment for the nine patients with *EGFR* mutation prior to SCLC transformation was 14 months (range, 7–21 months). Four patients (40%) had the same site of neoplastic transformation as the primary, and tissue biopsies were performed in six patients to confirm transformation in the metastases (60%). The images before and after transformation for case 4 are shown in *Figure 2*. In addition, NSE levels in 10 patients were all elevated before transformation (100%), and the fold elevation was 1.1 to 8.2, with an average elevation of 4.1 (3.5±2.8). Disease progression occurs primarily at multiple sites prior to transformation, including the lung, bone, brain, pleura, and lymph nodes. Eight patients maintained the original *EGFR* gene mutation type (80%) after transformation, but the mutation type of one patient changed to *EGFR* T790M mutation. Notably, the patient in case 10 with no *EGFR* mutation before transformation presented an *EGFR* E19 mutation after transformation. Relevant information for all patients is detailed in *Table 1*.

Pathological immunohistochemistry

Immunohistochemistry after transformation showed positive thyroid transcription factor 1 (TTF1), synaptophysin (Syn), CD56, AE1/AE3, negative Napsin A, highly expressed Ki67, and 0% expressed PD-L1 in all patients (*Table 3*, *Figure 3*). In addition, specimens of 5 cases were negative for chromogranin A (CgA).

The time interval of transformation

The time intervals between treatment and transformation from lung adenocarcinoma to SCLC were 7–40 months (median 24 months) in the 10 patients. In particular, the time interval to transformation for case 10 who did not receive targeted therapy was 34 months. The remaining 9 patients received targeted therapy before transformation. In terms of treatment sequence, 3 patients (cases 1, 2 and 8)

Table 1 Basic clinical characteristics of 10 patients with lung adenocarcinoma transforming to SCLC

Case No.	Gender	Age (years)	Smoking history	Staging	Mutation status of the initial diagnosis (test specimens)	TKI therapy line before transformation	Time interval from treatment to transformation (months)	Site of SCLC (relationship with primary tumor)	NSE level before transformation (multiples of increase)	Progression site before transformation	T790M mutation before transformation	Mutation status after transformation (test specimens)
1[a]	Male	58	No	IIIA	EGFR + exon 19 (tissue)	3rd line	17	Left lung (different part)	Increase (2.6)	Lung, bone, brain, abdominal lymph nodes	No	EGFR + exon 19 (tissue)
2[a]	Female	64	No	IIIB	EGFR + exon 19 (tissue)	3rd line	21	Liver (different part)	Increase (4.3)	Brain, liver, and abdominal lymph nodes	No	EGFR + exon 19 (tissue)
3	Male	56	No	IVA	EGFR + exon 19 (tissue)	1st, 2nd line	17	Right cervical lymph node (different part)	Increase (1.1)	Cervical lymph nodes	Yes	EGFR + exon 19 (tissue)
4	Male	54	Yes	IVB	EGFR + exon 19 (tissue)	1st line	13	Right pleura (different part)	Increase (2.1)	Pleura, lung, bone, mediastinal lymph nodes	Unknown	T790M (tissue)
5	Female	65	No	IVB	EGFR + exon 19 (tissue)	1st, 2nd, 3rd line	13	Right lung (same part)	Increase (1.1)	Lung	No	EGFR + exon 19 and PIK3CA (blood)
6	Male	30	No	IVB	EGFR + exon 19 (tissue)	1st, 2nd line	14	Right axillary lymph node (different part)	Increase (7.1)	Lung, bone, brain, pleura, mediastinum, axillary and abdominal lymph nodes	Yes	EGFR + exon 19 (blood)
7	Female	68	No	IVA	EGFR + exon 21L858R (tissue)	1st, 3rd, 4th line	14	Left lung (same part)	Increase (7.5)	Lung, brain, pleura, mediastinal lymph nodes	No	EGFR + exon 21L858R (blood)
8[a]	Male	59	No	IA	EGFR + exon 19 (tissue)	5th line	20	Left adrenal gland (different part)	Increase (8.2)	Adrenal gland	No	EGFR + exon 19 (tissue)

Table 1 (*continued*)

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Case No.	Gender	Age (years)	Smoking history	Staging	Mutation status of the initial diagnosis (test specimens)	TKI therapy line before transformation	Time interval from treatment to transformation (months)	Site of SCLC (relationship with primary tumor)	NSE level before transformation (multiples of increase)	Progression site before transformation	T790M mutation before transformation	Mutation status after transformation (test specimens)
9	Male	30	Yes	IVB	EGFR + exon 19 (tissue)	1st line	7	Right lung (same part)	Increase (5.4)	Lung, pleura, mediastinal lymph nodes	No	EGFR + exon 19 (blood)
10	Male	66	No	IIIA	No mutations (blood)	Not be applied	0	Right lung (same part)	Increase (1.3)	Lung, brain, abdominal lymph nodes, peritoneum	Unknown	EGFR + exon 19 (tissue)

[a], the patient has a history of resection of lower lobe of left lung. SCLC, small cell lung cancer; TKI, tyrosine kinase inhibitor.

were treated with chemotherapy followed by targeted therapy (C + T) and their time intervals to transformation were 38, 40 and 31 months (mean 36 months), respectively. The group treated with targeted therapy followed by chemotherapy (T + C) included cases 4, 5 and 7, whose time intervals to transformation were 13, 14, and 40 months (mean 22 months), respectively. In addition, 2 patients (cases 6 and 9) received concomitant chemotherapy combined with targeted therapy (CCT), and their transformation intervals were 15 and 7 months (mean 11 months), respectively. Besides, one patient (case 3) underwent targeted therapy alone and his transformation time was 17 months (*Table 4*). In brief, the C + T group demonstrated longer interval of transformation.

The treatment and prognosis after transformation

The therapeutic methods after transformation were mainly chemotherapy-based comprehensive treatment. As of August 1, 2020, seven patients had died, including two (cases 6 and 7) from brain metastases, four (cases 2, 4, 5 and 8) from liver metastases and one (case 10) from respiratory failure due to multiple lung metastases. For the seven patients who have died, the survival time after transformation was 6–13 months (median 10 months). PFS for all patients after transformation was 1–12 months (median 5 months after SCLC diagnosis) (*Table 5*).

Discussion

After receiving first-line EGFR-TKI treatment, the majority of advanced NSCLC patients with sensitive mutations in the *EGFR* gene would develop disease progression after 10 to 12 months, i.e., acquired resistance (2). The resistant phenotypes in 4% to 14% of patients are due to SCLC transformation (8). However, there is currently no clear consensus on the definition of transformation from lung adenocarcinoma into SCLC, and the mechanisms of drug resistance caused by SCLC transformation remain obscure. The prevailing view is that there may be three related mechanisms: (I) hypothesis of tumor cell heterogeneity: in the initial process of tumorigenesis, there are two mixed components in tumor tissue. SCLC and adenocarcinoma cells coexist in the same or different sites. The adenocarcinoma cells are the dominant component at initial period, under treatment EGFR-sensitive clones are constrained and instead SCLC clones expand and result in a majority SCLC histological subtype. (II) Hypothesis of tumor stem cell: tumor stem cells with sensitive mutation

Table 2 The treatment methods of 10 patients with lung adenocarcinoma before SCLC transformation

Case No.	Surgery	Targeted therapy	Chemotherapy	Radiotherapy	Bisphosphonate
1	▲ [1]	▲ [3]	▲ [2]	△	△
2	▲ [1]	▲ [3]	▲ [2]	▲ [3]	△
3	△	▲ [1.2]	△	△	△
4	△	▲ [1]	▲ [2]	▲ [1]	▲ [1]
5	△	▲ [1.2.3]	▲ [4]	△	△
6	△	▲ [1.2]	▲ [1]	▲ [2]	▲ [1]
7	△	▲ [1.3.4]	▲ [2.6]	▲ [5]	△
8	▲ [1.3]	▲ [5]	▲ [2]	▲ [4]	▲ [2]
9	△	▲ [1]	▲ [1]	▲ [1]	△
10	△	△	▲ [1.2]	▲ [2]	△

▲ means yes, △ means no, the numbers in [ ] are the order of treatment plan. SCLC, small cell lung cancer.

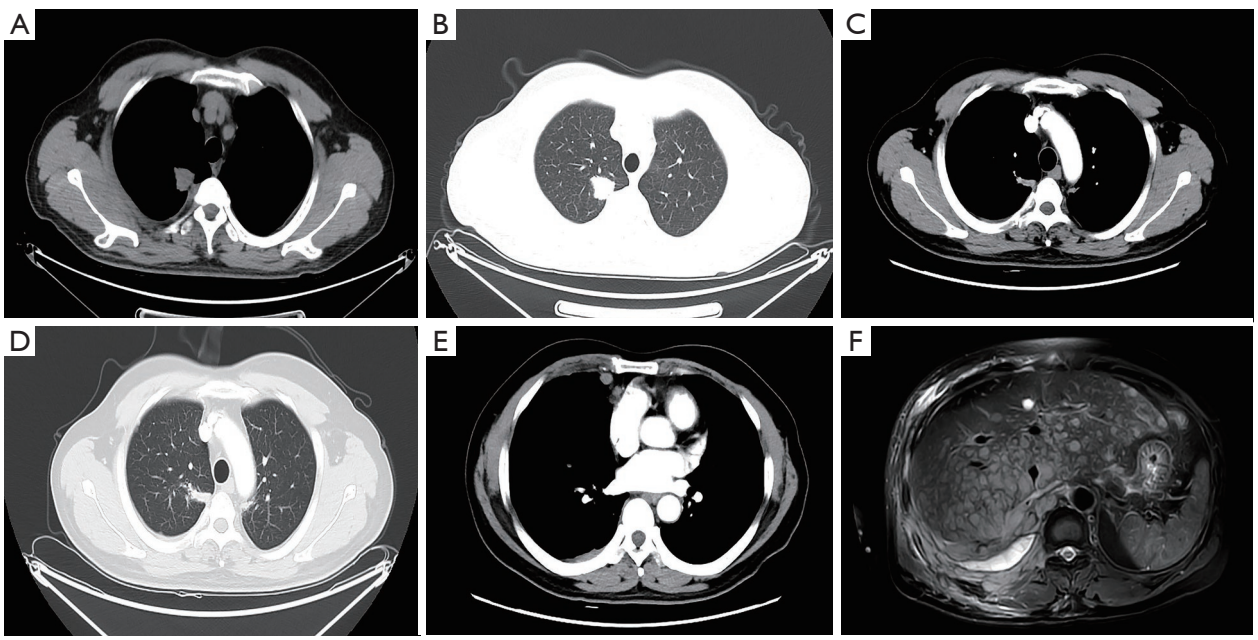

Figure 2 Images of case 4 at initial diagnosis and after transformation. (A) Chest CT in mediastinal window at initial diagnosis (adenocarcinoma). (B) Chest CT in pulmonary window at initial diagnosis (adenocarcinoma). (C) Chest CT in mediastinal window after transformation (SCLC). (D) Chest CT in pulmonary window after transformation (SCLC). (E) CT manifestations of pleural metastases after transformation (SCLC). (F) MRI manifestations of liver metastases after transformation (SCLC). CT, computed tomography; SCLC, small cell lung cancer; MRI, magnetic resonance imaging.

have the potential to differentiate into neuroendocrine tumor cells, EGFR TKIs select for EGFR-resistant clones in the adenocarcinoma that then subsequently transform into SCLC. (III) Hypothesis of molecular mechanism: during the treatment of TKIs, dual deletion mutations of tumor suppressor genes *RB1* and *TP53* appear, and they play an important role in SCLC transformation. Nowadays, more and more researchers are inclined to the second view. Sequist *et al.* performed second biopsies on patients diagnosed with lung adenocarcinoma with *EGFR*

Table 3 The expression of pathological immunohistochemical indicators after SCLC transformation

Case No.	TTF1	Napsin A	Syn	CD56	Ki67	CgA	AE1/AE3	PD-L1
1	(+)	(–)	(+)	(+)	70%+	(+)	(+)	(–)
2	(+)	(–)	(+)	(+)	90%+	(+/–)	(+)	(–)
3	(+)	(–)	(+)	(+)	70%+	(–)	(+)	(–)
4	(+)	(–)	(+)	(+)	80%+	(–)	(+)	(–)
5	(+)	(–)	(+)	(+)	80%+	(–)	(+)	(–)
6	(+)	(–)	(+)	(+)	80%+	(+)	(+)	(–)
7	(+)	(–)	(+)	(+)	90%+	(+)	(+)	(–)
8	(+)	(–)	(+)	(+)	80%+	(+)	(+)	(–)
9	(+)	(–)	(+)	(+)	70%+	(–)	(+)	(–)
10	(+)	(–)	(+)	(+)	80%+	(+)	(+)	(–)

"+" means positive; "–" means negative. TTF1, thyroid transcription factor 1; Syn, synaptophysin; CgA, chromogranin A; SCLC, small cell lung cancer; PD-L1, programmed cell death-ligand 1.

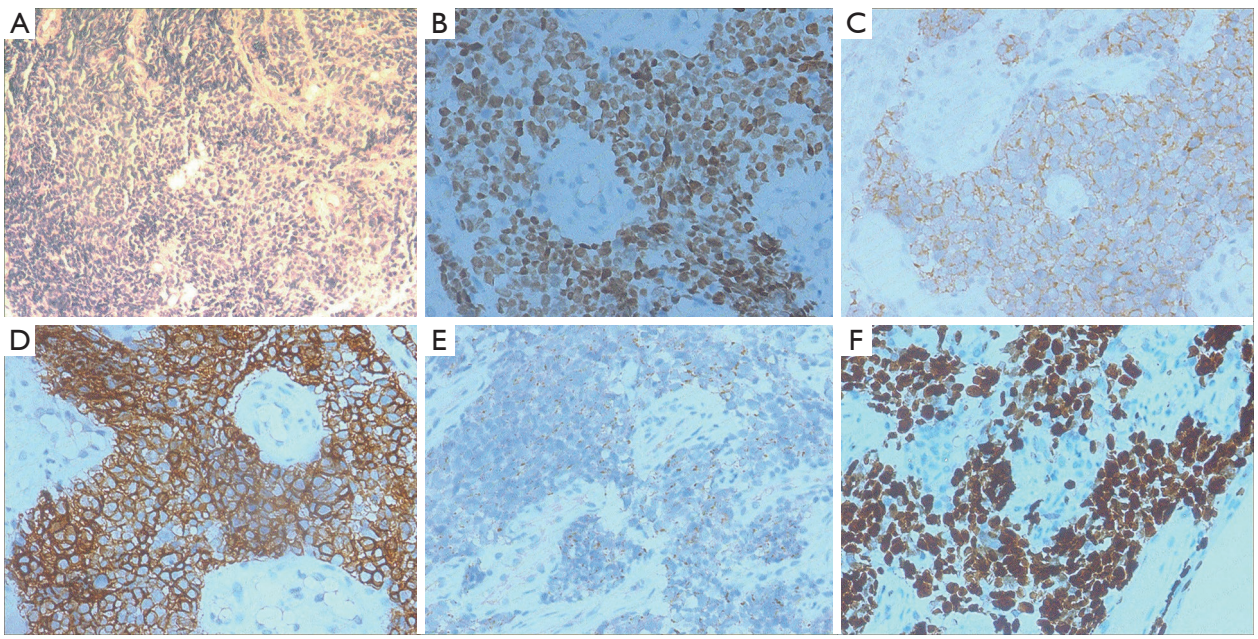

Figure 3 Pathological and immunohistochemical examination of case 1 after transformation (SCLC). (A) Pathology after transformation (H&E, ×10). (B) TTF-1 positive (IHC, ×20). (C) Syn positive (IHC, ×20). (D) CD56 positive (IHC, ×20). (E) CgA positive (IHC, ×20). (F) Ki67 high expression (IHC, ×20). H&E, hematoxylin-eosin staining; IHC, immunohistochemical staining; TTF-1, thyroid transcription factor 1; Syn, synaptophysin; CD56, nerve cell adhesion molecule CD56; CgA, chromogranin A; Ki67, Ki67 antigen.

gene mutation and resistance to targeted therapy (8). The results showed that the pathological types have transformed into SCLC, and the transformed SCLC tissues still maintained the original *EGFR* mutation type, suggesting that it may have originated from the same consistency tissues. Shi *et al.* showed that patients generally possessed consistent types of *EGFR* mutation before and after transformation, indicating that SCLC after TKI treatment originated from adenocarcinoma (9). Our findings that 8 of 10 patients who maintained the original *EGFR* gene

Table 4 The transformation interval of different treatment sequence groups

The therapeutic sequence before transformation	Case	The time interval of transformation [mean] (months)
C + T	1, 2, 8	38, 40, 31 [36]
T + C	4, 5, 7	13, 14, 40 [22]
CCT	6, 9	15, 7 [11]

C + T, chemotherapy followed by targeted therapy; T + C, targeted therapy followed by chemotherapy; CCT, concurrent chemotherapy combined with targeted therapy.

Table 5 Time to SCLC transformation, treatment, and outcome of 10 patients after SCLC diagnosis

Case No.	Time to SCLC transformation (months)	Treatment options for SCLC after transformation	Survival status	PFS after transformation (months)	Survival time after transformation (months)
1	38	Chemotherapy[b] + Radiotherapy, targeted therapy	Survive	12	--
2	40	Chemotherapy[b] + targeted therapy	Death	5	8
3	17	Chemotherapy[b], chemotherapy + targeted therapy, chemotherapy + immunity therapy	Survive	1	--
4	13	Chemotherapy[b] + targeted therapy, radiotherapy + chemotherapy + anti-angiogenic therapy, targeted therapy, radiotherapy + chemotherapy + immunity therapy	Death	11	13
5	14	Chemotherapy[b] + targeted therapy, radiotherapy, targeted therapy, chemotherapy	Death	5	10
6	15	Chemotherapy[b], radiotherapy	Death	5	8
7	40	Chemotherapy[b], chemotherapy + targeted therapy	Death	6	6
8	31	Chemotherapy[b]	Death	7	13
9	7	Chemotherapy[b]+ targeted therapy, radiotherapy, targeted therapy	Survive	2	--
10	34	Targeted therapy, chemotherapy[b]	Death	1	10

[b], the regimen of EP (etoposide plus cisplatin) is the first choice for post-transformation chemotherapy. "--" means that the patient is alive. SCLC, small cell lung cancer.

mutation after transformation are largely compatible with the two aforementioned studies. Although case 10 presented an *EGFR* E19 mutation at the second examination, this difference may be attributed to inconsistency in the testing subjects as the specimens for genetic testing were blood and tissue before and after transformation, respectively.

Marcoux *et al.* retrospectively reviewed 67 patients with *EGFR* mutant SCLC and other high-grade neuroendocrine carcinomas (10). Among them, *EGFR* mutations included exon 19 deletion (69%), L858R (25%), and others (6%). At the initial lung cancer diagnosis, 58 patients had NSCLC and nine had *de novo* SCLC or mixed histology. All these nine patients were treated with one or more TKIs prior to transformation. After transformation, both platinum etoposide and taxanes yielded high response rates, whereas the median PFS was only 3.4 months (2.4 to 5.4 months), and the median survival was only 10.9 months (8.0 to 13.7 months). The results of Ahmed *et al.* showed that the median time to transformation was 36 months in 30 patients with lung adenocarcinoma who received multiple lines of therapy (11). Besides, Roca *et al.* reported that the median time from initial diagnosis of lung adenocarcinoma to SCLC transformation was 19 months, and the median survival time after SCLC diagnosis was

6 months (12). Furthermore, Ferrer *et al.* found that patients with *EGFR* mutant NSCLC were more likely to develop SCLC transformation after multi lines of therapy, and that the majority retained a consistent mutation type (13). Our results are similar to those of the mentioned studies and suggest that aggressive second biopsy and genetic testing for patients with lung adenocarcinoma whose diseases progress after resistance to EGFR-TKI therapy or multiple lines of therapy are clinically warranted to select appropriate therapeutic strategies.

None of the 10 patients in this study was older than 70 years, with a mean age of 55 years. Studies have shown that elderly patients (≥65 years) with advanced NSCLC harboring EGFR sensitive mutations demonstrated longer PFS after EGFR-TKI treatment than younger patients (14,15), which may be attributed to the slow metabolism and corresponding alleviated tumor progression in the elderly. In recent years, many studies have shown that EGFR-TKIs in combination with chemotherapy can delay drug resistance and prolong PFS and OS in patients with *EGFR* mutation-positive advanced NSCLC (16-19). Some researchers have reported a correlation between gene expression and sensitivity to cancer agents in cell line models (20,21). In addition, patients with lung adenocarcinoma who received chemotherapy followed by targeted therapy exhibited a longer time interval of transformation than patients who received targeted therapy first. These findings suggest that perhaps chemotherapy delays the alteration of resistance related genes, but the mechanism requires further investigation.

NSE, a highly specific and sensitive tumor marker, plays a critical role in the diagnosis of SCLC (22). We observed an increase in NSE level in this study, indicating that NSE can be considered as a detection indicator. If patients' NSE increased with short-term and multi-site progression, attention should be paid to the possibility of SCLC transformation. The chemotherapy regimen of EC (etoposide plus carboplatin) or EP (etoposide plus cisplatin) in combination with immunosuppressive therapy has become the first choice for extensive staging SCLC (23,24). PD-L1 was not expressed in ten patients in this study, and two of them failed to undergo immunotherapy in subsequent treatments after transformation. In the study by Marcoux *et al.*, immune checkpoint inhibitors were ineffective in 17 patients (10), indicating that metrics to screen specific populations suitable for immunotherapy after transformation require further exploration.

There are certain limitations to this study. We did not test the *RB1* and *TP53* status in any of the patients at the first visit. For lung adenocarcinoma patients treated with EGFR-TKI, evaluating the *RB1* and *TP53* status is of great significance for predicting the occurrence and prognosis of SCLC transformation. Lee *et al.* in 2017 found a 42.8-fold increased relative risk of *EGFR* mutant lung adenocarcinoma with *RB1* and *TP53* inactivation at first diagnosis (25). In 2019, Offin *et al.* at the Sloan Kettering Cancer Center analyzed 43 patients with *EGFR/TP53/RB1* triple mutations, including 7 (18%) patients with lung adenocarcinoma who developed SCLC transformation during treatment (26). The median time from initial TKI treatment to transformation was 1.1 years, whereas patients with triple mutations had even shorter intervals.

As biopsy technology advances and genetic testing technology matures, more and more cases of SCLC transformation after lung adenocarcinoma treatment will be identified. In clinical work, awareness of secondary biopsies should be increased and whole-genome sequencing could be performed depending on the severity of the diseases, in hopes of earlier detection of SCLC transformation and development of a precise treatment strategy.

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Footnote

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uniform disclosure form (available at https://dx.doi.org/10.21037/tcr-21-653). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee board of the Fourth Hospital of Hebei Medical University (2020KY254) and individual consent for this retrospective analysis was waived.

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