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Anticancer Original Research Paper

Anlotinib as a post-third-line therapy for the treatment of advanced nonsmall cell lung cancer

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There is no standard treatment strategy for the third-line and above treatment of advanced nonsmall cell lung cancer (NSCLC). This study aimed to investigate the effects of anlotinib in patients with NSCLC. Data was collected from a group of advanced lung cancer patients who received anlotinib as a third-line or post-third-line treatment between 2017 and 2019. The Kaplan–Meier method was used to calculate the progression-free survival (PFS) of these lung cancer patients treated with anlotinib. Univariate analysis was performed using the log-rank test. Forest plot was used for subgroup analysis.Our study included 44 patients. Oral anlotinib was used as a third-line treatment to treat 26 patients, and as a fourth-line or multiline treatment in 18 patients. The objective control rate was 5%, the disease control rate was 89%, and the median PFS was 4.0 months with a 95% confidence interval. Common toxicities included anorexia, hypertension, and fatigue. Anlotinib demonstrated promising efficacy and was well tolerated with controlled toxicity in patients with NSCLC.

Keywords: lung cancer, anlotinib, angiogenesis, third-line, treatment, advanced cancer, nonsmall cell lung cancer

Introduction

The number of individuals living with lung cancer is relatively high, and the mortality rate is higher than that of other tumor types.[1] Most patients with lung cancer quickly relapse and succumb to the disease due to systemic metastasis after receiving the first-line chemotherapy.[2] The rapid development of targeted therapy, immunotherapy, and antitumor angiogenesis therapy has improved the survival of patients diagnosed with advanced lung cancer Patients diagnosed with either NSCLC or small cell lung cancer (SCLC) may receive third-line treatments and beyond. Anlotinib is a multitargeted tyrosine kinase inhibitor that has inhibitory effects on angiogenesis and tumor cell growth by targeting the vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and tyrosine kinase (c-Kit).[3] Clinical trials studying anlotinib were performed investigating a wide range of cancers, such as NSCLC, SCLC, soft tissue sarcoma (STS), renal cell carcinoma, hepatocellular carcinoma, esophageal squamous cell carcinoma, and nodules, rectal cancer, gastric cancer, medullary thyroid cancer and ovarian cancer. Preliminary studies showed that anlotinib has excellent potential for the multiline treatment of metastasized tumors.[4–8] In particular, the ALTER-0303 Phase II and Phase III studies that analyzed the third-line treatment of anlotinib in patients with NSCLC confirmed its effectiveness and safety.[9,10] The efficacy of anlotinib as a therapy for the third line or beyond for SCLC was also confirmed in the ALTER1202 trial.[11] However, there are no standard treatments for patients with NSCLC and SCLC beyond third-line therapy. Hence, we conducted a retrospective analysis to assess anlotinib as a third-line and post-third-line treatment for advanced NSCLC.

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Table 1. Patient characteristics.

Characteristics	*N* (%)
Patients enrolled	44
Gender, *n* (%)	
Males	32 (73%)
Females	12 (27%)
Median age (range), years	66 (35-86)
Baseline ECOG PS, n (%)	
0–1	13 (30%)
≥2	31 (70%)
Histology, *n* (%)	
Adenocarcinoma	30 (68%)
Squamous cell carcinoma	14 (32%)
EGFR status, *n* (%)	
Mutation	13 (30%)
Wild type/unknown	31 (70%)
Line of anlotinib	
Third line	26 (59%)
Further line	18 (41%)
Prior chemotherapy	
Used antitumor angiogenesis	21 (48%)
Unused antitumor angiogenesis	23 (52%)
Prior immunotherapy	
Yes	7 (16%)
No	37 (84%)

Abbreviation: ECOG PS, eastern cooperative oncology group performance status; EGFR, epidermal growth factor receptor.

Materials and methods

Patients

Data was collected from stage IV NSCLC patients enrolled at Nanjing Chest Hospital from 2017 to 2019. The main inclusion criteria were (1) NSCLC confirmed by histopathology, (2) stage IVNSCLC diagnosed through systemic evaluation and, (3) patients who received at least two lines of chemotherapy or targeted therapy. According to the evaluation criteria, patients needed to have at least one measurable lesion and have a continuous treatment follow-up.

Based on these criteria, 44 patients were enrolled in our study and all patients received anlotinib at a dose of 12 mg per day.

Study assessment

All patients received a comprehensive evaluation every 6 weeks until the tumor progressed using magnetic resonance imaging (MRI) and/or computer tomography (CT), blood tumor indicators, and other assessments of the condition, according to RECIST evaluation of efficacy. Complete response (CR) indicated that all lesions disappeared. Partial response (PR) indicated that target lesion's longest diameter was reduced by at least 30%. Stable disease (SD) indicated that target lesion's longest diameter was less than 20% or decreased to less than 30%. Progressive disease (PD) indicated that target lesion's longest diameter increased by at least 20%, or a new lesion appeared. Adverse drug reactions were evaluated according to the 3.0 version of the Common Terminology Criteria for Adverse Events version 3.0.

Table 2. Treatment efficacy in patients with anlotinib.

Clinical outcomes	All ($n = 44$)
Response rate	
CR	0
PR	2 (5%)
SD	37 (84%)
PD	5 (11%)
PFs (months)	4.0 (2.92–5.08)
OS (months)	8.5 (7.12–9.88)
DCR	89%
ORR	5%

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; OS, overall survival; DCR, disease control rate; ORR, objective response rate.

PFS refers to the time between the start of anlotinib treatment and the disease's progression. Overall survival (OS) was defined as the time from the first day of anlotinib treatment to death or last follow-up. Follow-up extended to September 1, 2020.

Statistical analysis

SPSS v.19.0 and Stata12.0 statistical softwares were used for analysis. Survival analyses were performed using the Kaplan–Meier method, and the log-rank method and forest plot were used for univariate analysis of PFS and OS. Statistical significance was defined as $P < 0.05$.

Results

Patient characteristics

The median age of the 44 patients was 66 years (35–86), and the majority of patients were male (32/44, 73%). A total of 35 patients had an ECOG performance status score of ≥2 (31/44, 70%). Thirty patients had adenocarcinoma (30/44, 68%), 14 patients had squamous cell carcinoma (14/44, 32%). There were 13 patients with epidermal growth factor receptor (EGFR) gene mutations (13/44, 30%). Anlotinib was used as a third-line treatment for 26 patients and as a fourth-line or beyond treatment in 18 patients. Before treatment with anlotinib, 21 patients were treated with angiogenesis-targeting drugs, such as bevacizumab or recombinant human endostatin, and seven patients were treated with immunotherapy. The demographic characteristics of the enrolled patients are listed in Table 1.

Treatment efficacy

The enrolled patients received anlotinib monotherapy at a dose of 12 mg per day. If toxicity

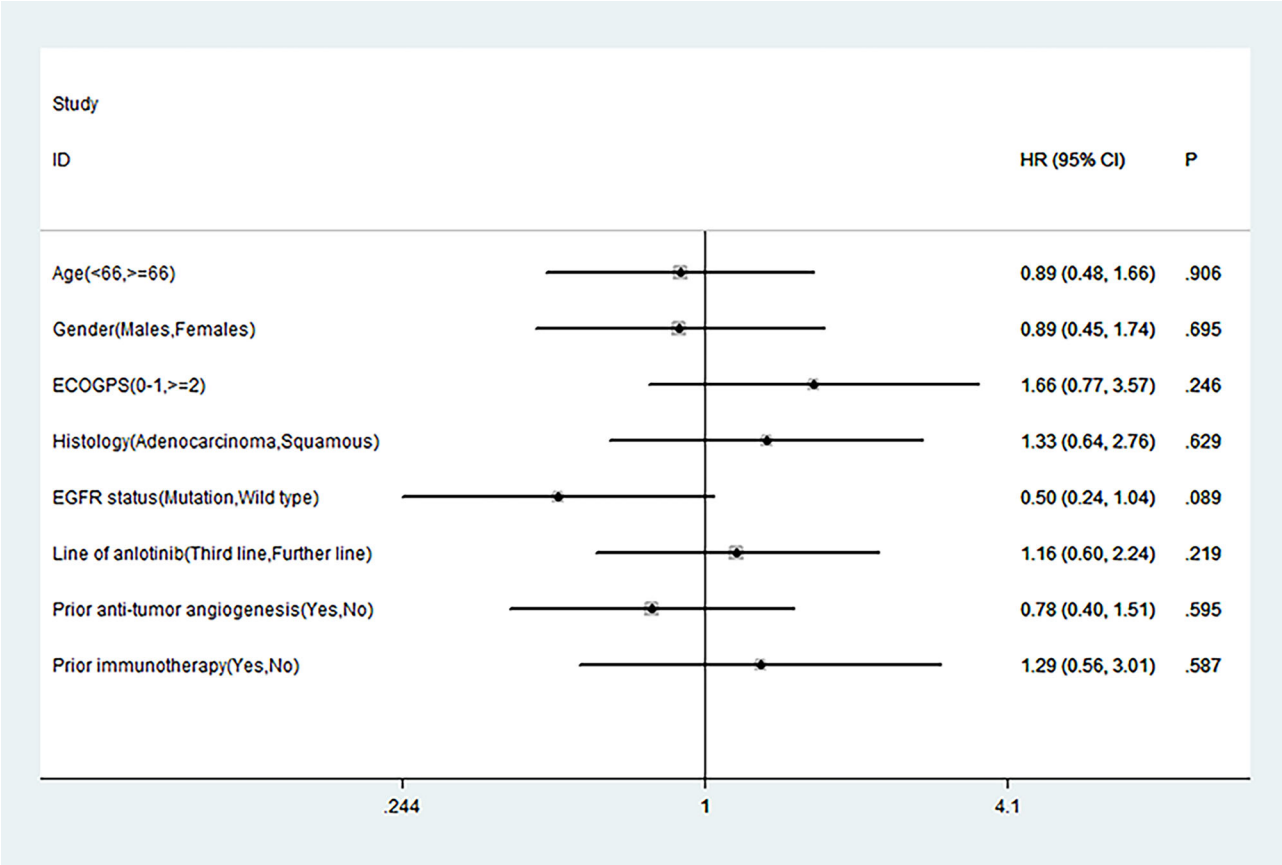

Figure 1. Prognostic factors associated with the progression-free survival after the administration of anlotinib. HR, hazard ratio; CI, confidence interval; *P*, *p* value.

intolerance was observed, the dose was reduced to 10 mg per day. The short-term efficacy was evaluated using the international standard RECIST criteria. There were no patients with CR, two patients had a PR, 37 patients had SD and five patients experienced PD. Patients had a median PFS (mPFS) of 4.0 months and a median OS (mOS) of 8.5 months. The objective response rate (ORR) was 5%, and the disease control rate (DCR) was 89% (Table 2).

Univariate analysis

Using univariate analysis, a detailed PFS and OS correlation analysis was conducted from patient characteristics including gender, age, pathological type, ECOG performance status, genetic testing status, whether it was third-line or multiline treatment and whether or not antitumor angiogenesis drugs or immunotherapy were used. Based on this analysis, the mPFS and mOS of male patients were longer than that of female patients, the mPFS and mOS of patients with an ECOG performance status of 0–1 were longer than those with scores 2–3. For patients with EGFR genetic mutations, the mPFS was better than patients with wild-type tumors, and the mOS of patients without mutations was longer. The mOS of patients treated with anlotinib as a third-line treatment was significantly better than patients who received anlotinib as the fourth-line or beyond ($P < 0.05$) (Figures 1 and 2).

Survival estimates

The mPFS for all patients was 4.0 months (95% CI: 2.92–5.08), and the mOS was 8.5 months (95% CI 7.12–9.18) (Figure 3).

Drug toxicity

Toxicity was assessed in all patients, and no treatment-related deaths were identified. The main adverse reactions were fatigue, anorexia, hand–foot syndrome, hypertension, bone marrow suppression, abnormal liver function, and diarrhea. Six cases (14%) of adverse events were above grade 3, and there were one cases of anorexia (2%), one case of hand–foot syndrome (2%), two cases of hypertension (5%), and two cases of fatigue (5%). All adverse effects were effectively controlled with symptomatic treatment or adjusted drug dosage (Table 3).

Discussion

Patients with lung cancer are often diagnosed at later stages of the disease, with no opportunity to receive effective surgery.[12] Multiple therapeutic

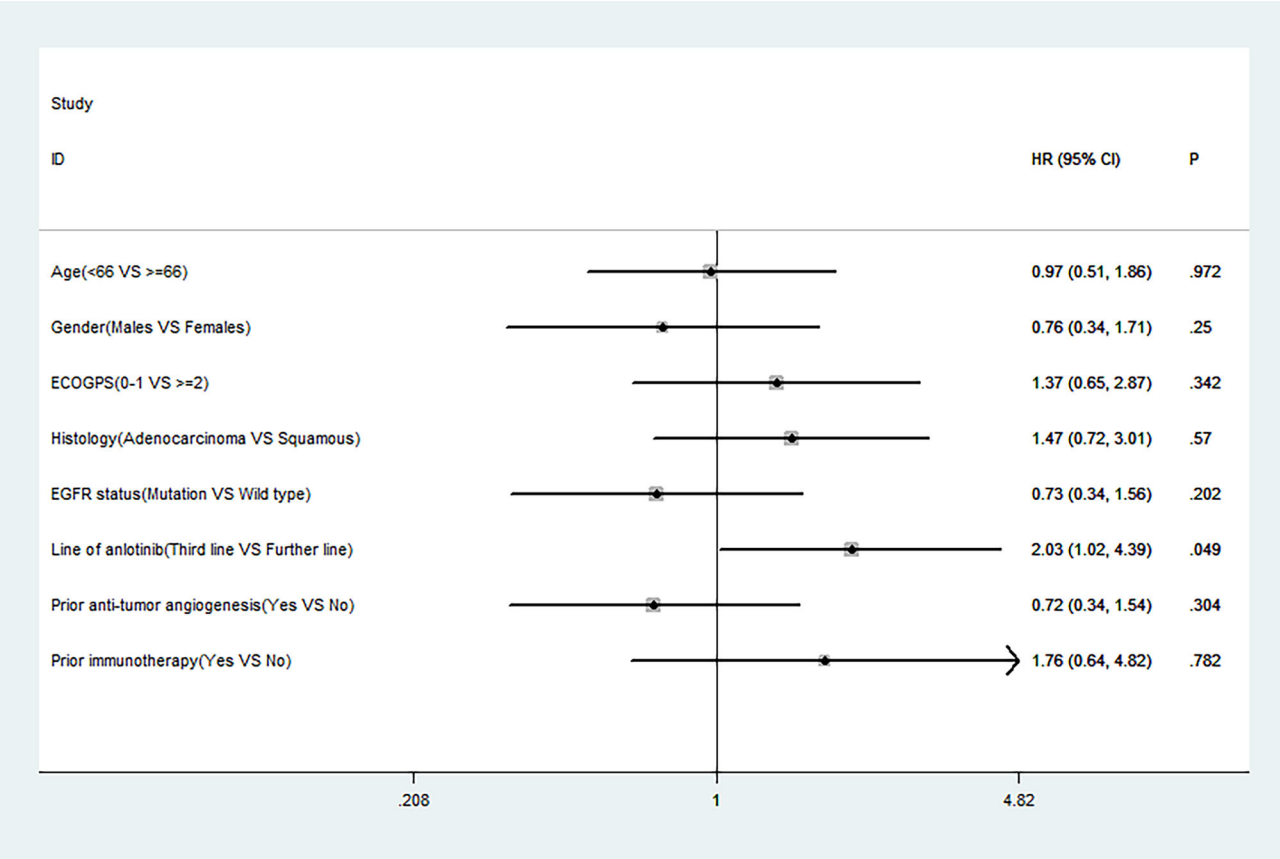

Figure 2. Prognostic factors associated with the overall survival after the administration of anlotinib. HR, hazard ratio; CI, confidence interval; *P*, *p* value.

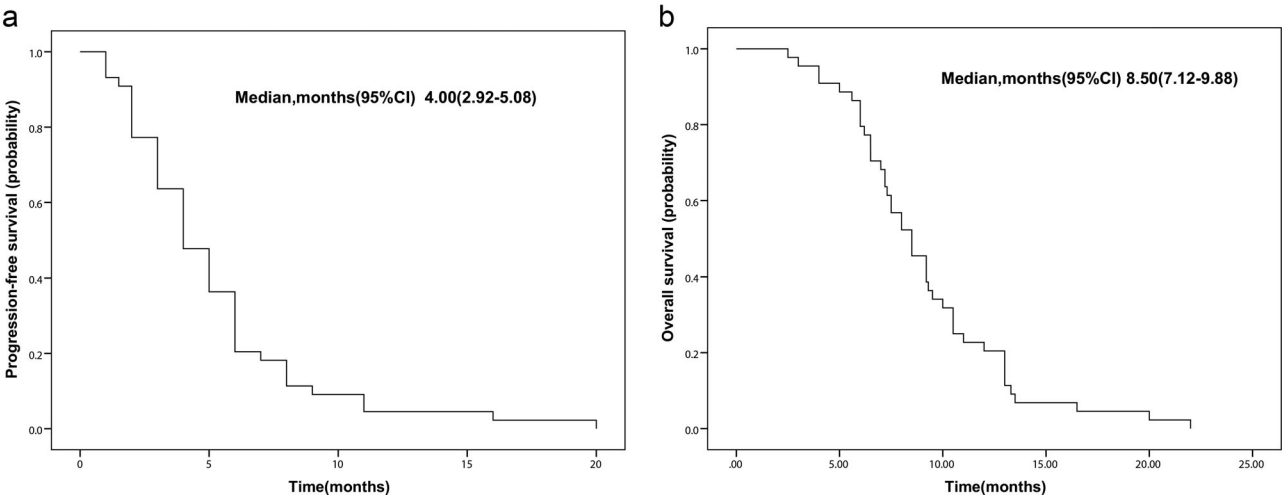

Figure 3. Progression-free survival and overall survival of patients who treated with anlotinib. (a) The median PFS, 4.0 months, 95% CI 2.92–5.08; (b) the median OS, 8.2 months, 95% CI 7.12–9.88.

strategies exist to treat advanced lung cancer, including targeted therapy, platinum-based chemotherapy, antitumor vascular therapy, and immunotherapy. There is an urgent need for effective third-line and beyond treatment. At this stage, the patient's ECOG performance status is low, and treatment is generally poorly tolerated. In this situation, the treatment strategy choice is crucial. Anlotinib is a new type of small-molecule tyrosine kinase inhibitor. Third-line treatment of anlotinib has a significant effect on NSCLC.[13–17] The drug contains dual functions in inhibiting tumor growth and blocking angiogenesis. It targets multiple oncoproteins involved in angiogenesis, such as VEGF, PDGF, FGFR, and the c-Kit pathway.[18]

To observe the efficacy and safety of third-line and fourth-line/beyond treatment of anlotinib for advanced NSCLC, we retrospectively analyzed 44 patients with advanced NSCLC, which30 cases were adenocarcinoma and 14 cases were squamous

Table 3. Drug reactions in the anlotinib.

Adverse drug reaction	1–2 grade [*N* (%)]	3–4 grade [*N* (%)]
Fatigue	26 (59%)	2 (5%)
Anorexia	26 (59%)	1 (2%)
Hand–foot syndrome	18 (41%)	1 (2%)
Diarrhea	12 (27%)	0 (0%)
Oral mucositis	6 (14%)	0 (0%)
Vomiting	3 (7%)	0 (0%)
Hypertension	20 (45%)	2 (5%)
Sinus tachycardia	4 (9%)	0 (0%)
Rash	6 (14%)	0 (0%)
Proteinuria	1 (2%)	0 (0%)
Hematuria	2 (5%)	0 (0%)
Thrombocytopenia	3 (7%)	0 (0%)
Leukopenia	5 (11%)	0 (0%)
Anemia	4 (9%)	0 (0%)
Elevated liver enzymes	10 (23%)	0 (0%)
Increased urea nitrogen High uric acid	2 (5%)	0 (0%)
	3 (7%)	0 (0%)
Abnormal blood coagulation	6 (14%)	0 (0%)

cell carcinoma. The ORR was 5%, the DCR was 89%, the mPFS was 4.0 months (95% CI: 2.92–5.08), and the mOS was 8.5 months (95%CI: 7.12–9.88).

The ALTER 0303 trial showed that patients treated with anlotinib had an mPFS of 5.4 months, which was significantly longer than the 1.4 months of the placebo group ($P < 0.001$). Compared with the placebo group, the ORR and DCR in the anlotinib group were also significantly higher at 9.2% vs. 0.7%; ($P < 0.001$) and 81.0% vs. 37.1%; ($P < 0.001$), respectively.[9] In the ALTER0303 trial, the mPFS of the placebo group and the anlotinib group were 2.7 m and 4.8 m ($P < 0.001$), respectively. The mOS was 6.5 months in the placebo group vs. 10.7 months in the anlotinib group ($P = 0.2570$).[19] These results showed that patients with advanced NSCLC and SCLC effectively respond to anlotinib treatment.

In this study, we evaluated the mPFS and mOS of patients with NSCLC, more specifically patients that were EGFR driver gene positive or negative, independent of antitumor angiogenesis drugs or immunotherapy were used in the past, and independent of patient ECOG performance status. For mPFS, there was no statistical difference between various influencing factors. However, patients with an ECOG performance status of 0-1 (5.00 vs. 4.00), those who were EGFR driver gene positive (3.00 vs. 4.00) and those who received third-line therapy (5.00 vs. 3.00) showed longer mPFS.

The mOS of patients with third-line therapy was significantly longer than patients with multiline therapy (9.20 vs. 7.20 months, $P = 0.049$). Other significant differences were observed for adenocarcinoma vs squamous cell carcinoma, driver genes, and antitumor angiogenesis. There was no statistical difference observed for drugs, immunotherapy, gender, age or ECOG performance status. Patients enrolled in our real-world group had much more advanced disease than the patients in the 0303 clinical trial study. There were 31 patients with an ECOG performance status of ≥ 2 and 18 patients who received post-third-line treatment. These patients still obtained satisfactory results, and anlotinib showed superior efficacy. In our study, the median survival after anlotinib treatment as a third-line treatment was longer, indicating that anlotinib maybe can achieve longer mOS as a second-line or even a first-line treatment.

Hypertension was the most common grade 3 adverse event observed during anlotinib treatment in a previous study.[20] In this study, hypertension (2/44; 5%) was the most common Grade 3 adverse event. In addition, other observed adverse events included anorexia (1/44; 2%), fatigue (2/44;5%), and hand–foot syndrome (1/44;2%). There were no interruptions in patient treatment due to any of these adverse events.

The adverse events of anlotinib in these patients were consistent with the ALTER-0303 and ALTER 1202 studies.[20] In a study by Chi et al.[21] anlotinib was investigated to treat refractory soft tissue sarcoma. The most common clinical grade 3 and above adverse events in this population were hypertension (4.8%), elevated triglycerides (3.6%), and pneumothorax (2.4%). There were no treatment-related deaths. Sun et al.[22] conducted an expanded cohort study to evaluate the role of anlotinib in patients with advanced refractory solid tumors. The study showed that the main severe adverse events were hypertension, elevated triglycerides, hand and foot skin reactions and increased lipase levels. Anlotinib has a controllable toxicity profile,

with a long-cycle and broad-spectrum antitumor potential. These studies have shown that the incidence of severe toxic side effects is relatively low.

Previous studies have assessed combination strategies in lung cancer treatment, including anlotinib combined with immunotherapy or anlotinib combined with chemotherapy.[23,24]

We recognize that our research has certain limitations, mainly due to the heterogeneous nature of the patients included in this study. Hierarchical analysis will require additional real-world research in the future.

Our results suggest that anlotinib is effective for the third-line or beyond treatment advanced NSCLC. It is well tolerated and did not result in any toxicity-related deaths. We will continue to follow-up and expand analyses for enrolled patients, further stratify group analysis, screen for baseline characteristics, guide clinical work, and look forward to including anlotinib in more clinical trials. Future research should be performed to explore the relevance of treatment modes and efficacy of different gene mutations.

Disclosure statement

The authors declare no conflict of interest.

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Ethics approval and consent to participate

This study was approved by the Ethics Clerk Association of the Thoracic Department of the Brain Hospital Affiliated to Nanjing Medical University. All aspects of the study are in line with the guidelines of the Declaration of Helsinki. In this study, all patients participated voluntarily, and all patient data were strictly confidential. Because it is a retrospective study, the Ethics Committee of the Thoracic Department of the Brain Hospital Affiliated to Nanjing Medical University has specifically approved it without written consent.

Data availability statement

All data are available by contacting correspondence authors: via: xuch2188@163.com

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