


Evaluating the Efficacy of EGFR-TKIs Combined With Radiotherapy in Advanced Lung Adenocarcinoma Patients With EGFR Mutation: A Retrospective Study

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Abstract

Objective: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have been recommended as the first-line treatment for advanced lung adenocarcinoma with epidermal growth factor receptor (EGFR) mutation. This study retrospectively evaluated patients' survival and related prognostic factors from single-center, real-world data. **Methods:** From January 2015 to December 2020, patients detected with EGFR mutation showing unresectable clinical stages III to IV advanced lung adenocarcinoma and receiving EGFR-TKIs and radiotherapy (RT) were recruited for the study. The overall survival (OS) and progression-free survival (PFS) were statistically analyzed with SPSS 22.0 software. **Results:** This study included 238 patients who completed their follow-up by December 30, 2020. The 1-, 2-, 3-year and median OS were 84.4%, 59.7%, 38.7%, and 30.3 months for OS, 57.0%, 28.8%, 15.7%, and 14.1 months for progression-free survival (PFS1), and 78.9%, 71.7%, 33.3%, and 25.0 months for PFS2, respectively. Multivariate analysis showed that, the independent factors for OS are age, clinical stage, the sequence of TKI and CT, and the total treatment response, and total response; the independent factors for progression-free survival I are clinical stage and total treatment response; the independent factors for PFS2 are clinical stage, type of TKI, sequence of TKI and CT, and total treatment response. The univariate analysis also showed a significant association between RT duration ($P=0.041$) and dose ($P=0.026$) with PFS1. **Conclusion:** EGFR-TKIs combined with RT was tolerable and efficient for patients with advanced lung adenocarcinoma. OS and PFS prove CT sequential with TKIs. Better treatment response with CR + PR was associated with a longer duration of OS, PFS1, and PFS2. However, further study is required in a larger sample size to confirm the results.

Keywords

lung adenocarcinoma, epidermal growth factor receptor, tyrosine kinase inhibitor, radiotherapy, chemotherapy, overall survival, progression-free survival

Abbreviations

19-Del, exon 19 deletions; 21-L858R, exon 21 L858R mutation; CCRT, concurrent chemoradiotherapy; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; IMRT, intensity-modulated radiation therapy; LAT, local ablative therapy; LCT, local consolidated therapy; LA-NSCLC, locally advanced NSCLC; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD, disease progression; PET/CT, positron-emission tomography; PFS, progression-free survival; PFS1,

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progression-free survival 1; PFS2, progression-free survival 2; PS, performance status; RT, radiotherapy; TKI, tyrosine kinase inhibitor; WBRT, whole-brain radiotherapy; WHO, World Health Organization

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Introduction

Cancer remains a global burden according to GLOBOCAN 2020 and has been reported as one of the leading causes of human mortality by the World Health Organization (WHO) in 2019. Lung cancer is the second-most diagnosed cancer and the leading cause of worldwide cancer-related deaths (11.4%).¹ Among the two subsets of lung cancers, non-small cell lung cancer (NSCLC) makes up approximately 80% to 85% of all lung cancer cases, predominantly and most frequently caused by lung adenocarcinoma accounting for 30%.² In clinical diagnosis, more than one-third of patients, present lung adenocarcinoma with a mutation in the epidermal growth factor receptor (*EGFR*) gene.³ Hence, sensitizing *EGFR* mutation consequently agitates the tyrosine kinase inhibitor (TKI), resulting in the phosphorylation of downstream signaling pathways and causing uncontrolled cell proliferation, invasion, and metastasis.⁴ The recommended gold standard treatment is first-generation epidermal growth factor receptor tyrosine kinase inhibitor (*EGFR*-TKI) for advanced adenocarcinoma NSCLC mutation in the *EGFR* gene). This therapy has resulted in significant improvements of 9 to 12 months in progression-free survival (PFS).^{5,6} Notably, TKI therapy can lead to remarkable survival benefits and elicits fewer toxic effects than conventional chemotherapy (CT). However, even after TKI therapy, most patients still face disease progression (PD). Hence, to overcome the reoccurrence of symptoms in patients with stage IV adenocarcinoma of the lung with *EGFR* mutation, several studies have investigated the survival benefits of TKI with local radiotherapy (RT)^{7–11} as a combinational therapy.

While concurrent chemoradiotherapy (CCRT) treatment is considered the standard strategy for unresectable patients diagnosed with locally advanced NSCLC (LA-NSCLC), the outcome remains unsatisfactory. In previous works, the value of TKIs was explored in patients with LA-NSCLC with *EGFR* mutation.^{11,12} Therefore, we planned and executed a retrospective study to examine the prognosis of patients with stages III to IV adenocarcinoma of the lung with *EGFR* mutation who received *EGFR*-TKIs and RT.

Patients and Methods

Patient Eligibility

For this retrospective analysis, patients were recruited only if they had clinical stages III to IV adenocarcinoma of the lung and mutation in the *EGFR* gene and had received combined therapy of *EGFR*-TKI with RT. Ethical committee approval was obtained from our hospital and written informed consent

was received from all patients between January 2015 and December 2021. In this study, eligible patients were confirmed to possess the pathological condition of lung adenocarcinoma with sensitizing mutation detected in *EGFR* (deletion of exon 19, mutation of exon 21, or others); diagnosed with stages III to IV according to the guidelines mentioned in the American Joint Committee on Cancer staging system (seventh edition) without surgery, as per the Eastern Cooperative Oncology Group (ECOG) guidelines; 18 years of age or older with a performance status (PS) score of 2 or less; and received the combined treatment of *EGFR*-TKI and local RT with or without CT. Further diagnosis of the tumor stage was performed using a systemic imaging technique through contrast-enhanced computed tomography. The chest, abdomen, and bones were scanned using positron-emission tomography (PET), and brain imaging was conducted either by contrast-enhanced computed tomography or magnetic resonance imaging (MRI). We have de-identified all patient details. All patients have signed the consent prior to treatment. The reporting of this study conforms to STROBE guidelines.¹³ This study was approved by the Ethics Committee of our hospital (2021KY253).

Treatment

The recommended generic drug for *EGFR*-TKI combination is 250 mg gefitinib once a day, 150 mg erlotinib once a day, 125 mg icotinib three times a day, and other TKI agents. An experienced radiotherapist decided on the dose fractionation regimen intending to cure the disease to the maximum possibility. RT approved by radiation oncologists included the standard-fractionation radiotherapy treatment for the primary tumor, whole-brain radiotherapy (WBRT), boost RT for local brain metastasis, and palliative RT for bone metastasis. Radiation was implemented mainly by intensity-modulated radiation therapy (IMRT) techniques. However, the evaluation of the treatment response was graded according to the guidelines mentioned in Response Evaluation Criteria in Solid Tumors version 1.1.

Statistical Analysis

The overall survival (OS) statistical calculation was done from the first treatment until death or alive (censored). PFS1 and PFS2 were calculated according to the time of first treatment until progression of the first or second time, until death or censored. The chi-square test was applied for counting data. Overall and PFS curves were estimated using the Kaplan–Meier product-limit method. A log-rank test was implemented to compare the survival functions

between the groups. The hazard ratio (HR) was calculated using the Cox regression model. Statistical significance was established for $P < .05$, and all the reported P values are two-sided.

Results

Clinical Characteristics of Patients

This study included 238 patients, including 101 males and 137 females, with a median age of 61 years (range: 21-86 years). Among these patients, 94 patients were detected to have EGFR mutation in 19 exon deletion (E19del), 118 patients had a mutation in 21 exons, and 26 patients had other point mutations. There were 33 patients (19.3%) in stage III, 84 (35.3%) in stage IVA, and 121 (50.5%) in stage IVB. A high chronological prevalence of bone metastases was observed in 125 patients (52.5%), followed by brain metastases in 115 patients (48.3%) and abdominal metastases in 43 patients (18.1%).

Treatment

The administered first-line EGFR-TKIs drugs were gefitinib (89 patients, 37.4%), icotinib (109 patients, 45.8%), erlotinib (29 patients, 12.2%), osimertinib (6 patients, 2.5%), and others (5 patients, 2.1%). Only 120 (52.5%) patients received EGFR-TKIs alone, whereas 118 patients accepted to undergo TKIs plus CT. Among those patients who received CT, 43 (18.1%) were recommended for TKIs concurrent with CT (defined as “TKI con CT”), 32 (13.5%) were given TKIs sequenced by CT (defined as “TKI seq CT”), and 43 (18.1%) were suggested to receive CT sequenced by TKIs (defined as “CT seq TKI”). Moreover, CT along with the platinum-based two-drug regimens was given to 100 patients (combined treatment with pemetrexed to 64 patients, paclitaxel to 19, docetaxel to 5, etoposide to 5, gemcitabine to 3, vinorelbine to 3, pemetrexed alone to 11, paclitaxel alone to 4, and other combinational drugs to 5 patients). The median No. of cycles of CT was 4 (range: 1-29); 31 patients underwent 1 cycle, 12 with 2 cycles, 9 with 3 cycles, 18 with 4 cycles, 6 with 5 cycles, 18 with 6 cycles, 21 with 7 to 12 cycles, and 4 with more than 12 cycles.

RT was performed after PD in 167 (70.2%) patients and 71 (29.8%) at the time of non-PD. Ninety-six patients were allowed

to undergo RT to cure the primary tumor. Sixty-four patients at the time of non-PD showing stage III—21 patients, IVA—24 patients, and IVB—19 patients were also suggested to receive RT. Similarly, 32 patients (8—stage III, 17—stage IVA, and 7—stage IVB) received RT after PD. The recommended median dose of RT was 60 Gy (range: 10-66 Gy). One hundred ten patients were counseled to take RT to treat brain metastasis, among whom 14 patients (8 in stages IVA and 6 in stage IVB) were at non-PD, and 96 patients (3 in stage III, 24 in stage IVA, and 69 in stage IVB) after PD received the median RT dose of 40 Gy (range: 12-66 Gy). Fifty-four patients accepted to take RT for bone metastasis, of whom 8 (5 in stage IVA and 3 in stage IVB) at non-PD and 46 patients (1 in stage III, 19 in stage IVA, and 26 in stage IVB) were after PD; and the median dose of RT was 30 Gy (range: 10-60 Gy). RT was performed in 218 patients in a single site (76 for primary tumor, 100 for brain, and 42 for bone metastasis), and 20 patients accepted to undergo RT at 2 sites (7 with primary tumor and brain metastasis, 12 with primary tumor and bone metastasis, and 1 with brain and bone metastasis.).

The Total Response of Treatment

The total response was evaluated in CR, PR, SD, and PD in 7, 107, 70, and 54 patients, respectively. The rate of CR + PR (ORR), SD, and PD for all patients was 47.9%, 29.4%, and 22.7%, respectively. The clinical stage and sequence of TKI with CT were correlated to determine the total response ($P < .01$, see Table 1). However, the total response with respect to gender ($P = .541$), age ($P = .453$), site of RT ($P = .341$), timing of RT ($P = .850$), type of EGFR mutation ($P = 0.280$), and the type of TKI agents ($P = .421$) remained insignificant.

Overall Survival

Until the end of the follow-up, 145 patients were deceased, and 93 were alive. The 1-, 2-, 3-, 4-, 5-year and median OS were 84.4%, 59.7%, 38.7%, 26.6%, 20.7%, and 30.3 (26.2 -34.5) months, respectively (Figure 1a). Univariate analysis of OS shows that age and clinical stage are significantly associated ($P < .05$). However, gender, type of EGFR mutation, type of TKI agents, sequence of TKI and CT, the timing of RT, site of RT, and the total treatment response are not associated with OS ($P > .05$);

Table 1. The Overall Response in Patients Having Lung Adenocarcinoma with Epidermal Growth Factor Receptor (EGFR) Mutation.

Items	Groups	Cases	CR + PR	SD	PD	<i>P</i> Value
Clinical Stage	III	33	7 (21.2%)	13 (39.4%)	13 (39.4%)	.004
	IVA	84	37 (44.0%)	27 (32.1%)	20 (23.8%)	
	IVB	121	70 (57.9%)	30 (24.8%)	21 (17.4%)	
Sequence of TKI and CT	TKI alone	120	72 (60.0%)	31 (25.8%)	17 (14.2%)	.004
	TKI Con CT	43	16 (37.2%)	12 (27.9%)	15 (34.9%)	
	TKI seq CT	32	9 (28.1%)	14 (43.8%)	9 (28.1%)	
	CT seq TKI	43	17 (39.5%)	13 (30.2%)	13 (30.2%)	

Abbreviations: CT, chemotherapy; Con, concurrent; seq, sequence; PD, disease progression; TKI, tyrosine kinase inhibitor.

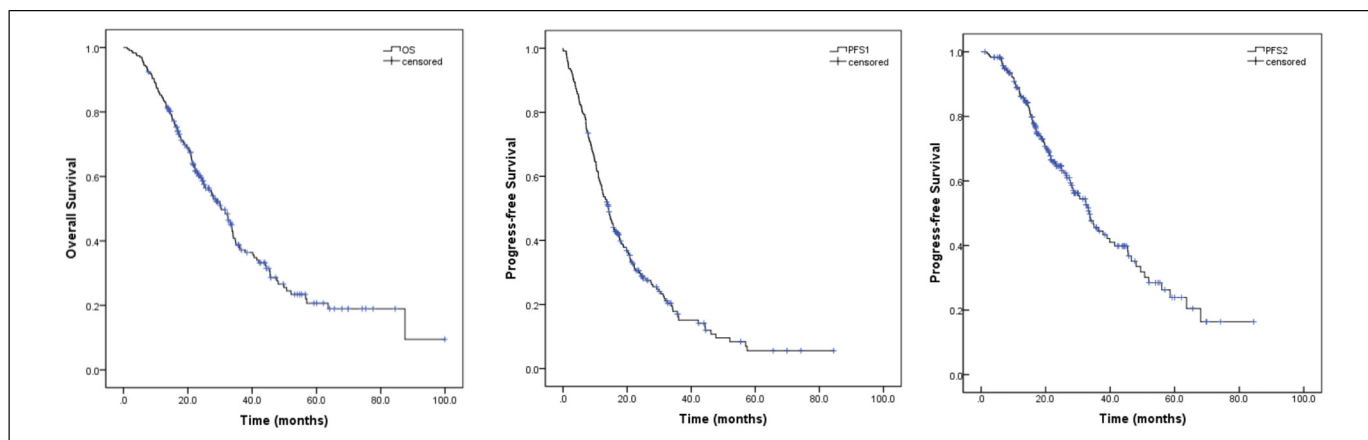


Figure 1. Survival curves of stage IV lung adenocarcinoma patients with epidermal growth factor receptor (EGFR) mutation: (a) Overall survival (OS); (b) progression-free survival 1 (PFS1); and (c) progression-free survival 2 (PFS2).

see Table 2. Based on the multivariate analysis, age, clinical stage, the sequence of TKI and CT, and the total treatment response were found to be the independent factors of OS, as shown in Table 3. The analysis of subgroup data indicates that OS exhibits a significant difference between stages IVA *versus* IVB ($P = .007$), TKI con CT *versus* CT seq TKI ($P = .013$), TKI seq CT *versus* CT seq TKI ($P = .050$), and CR+PR *versus* SD ($P = .031$), respectively.

Progression-Free Survival 1

The 1-, 2-, 3-, 4-, 5-year and median PFS1 were 57.0%, 28.8%, 15.7%, 9.4%, 5.5%, and 14.1 (12.1-16.2) months, respectively (Figure 1b). Univariate analysis reveals that the sequence of TKI and CT, timing of RT, and the total response are associated with PFS1 ($P < .05$). However, gender, age, stage, mutation types in EGFR gene various TKI agents, and site for RT do not have any association with PFS1. Data subjected to multivariate analysis indicate that clinical stage and total response are independent factors for PFS1. Subgroup analysis reveals that PFS1 shows a significant difference between RT for primary tumor *versus* RT for bone metastasis ($P = .034$), TKI alone *versus* TKI seq CT ($P = .007$), TKI seq CT *versus* CT seq TKI ($P = .034$), CR+PR *versus* SD ($P < .001$), and CR+PR *versus* PD ($P < .001$).

Progression-Free Survival 2

The 1-, 2-, 3-, 4-, 5-year and median PFS2 were 78.9%, 71.7%, 33.3%, 23.7%, 13.9%, and 25.0 months, respectively (Figure 1c). The univariate analysis demonstrates that the total response of treatment is associated with PFS2 ($P < .05$). Contrarily, gender, age, stage, type of EGFR mutation, type of TKI agents, sequence of TKI and CT, and the timing of RT are not associated with PFS2. Based on the multivariate analysis, clinical stage, type of TKI agents, sequence of TKI and CT, and the total response are independent factors for PFS2. Subgroup data analysis showed that PFS2 conferred a

significant difference between stage IVA *versus* IVB ($P = .023$), TKI con CT *versus* CT seq TKI ($P = .019$), TKI alone *versus* CT seq TKI ($P = .075$), gefitinib *versus* erlotinib ($P = .056$), gefitinib *versus* other TKI ($P = .050$), icotinib *versus* other TKI ($P = .075$), erlotinib *versus* icotinib ($P = .098$), CR + PR *versus* SD ($P = .001$), and CR + PR *versus* PD ($P = .003$).

Discussion

Treatment with first-line EGFR-TKI could significantly improve PFS but not OS in patients with advanced NSCLC showing EGFR mutation when compared with CT.^{5,6} Huang MY *et al* reported median values of OS and PFS in patients having advanced lung adenocarcinoma harboring EGFR mutation, for which 6230 patients received gefitinib for 24.2 and 11.7 months, while 2359 patients received erlotinib for 25.7 and 10.9 months, respectively.¹⁴ First-line icotinib was also administered at 11.3 months of PFS for lung adenocarcinoma patients at stage IIIB/IV detected with a mutation in the *EGFR* gene.⁶ However, most patients still experienced tumor progression after TKI treatment.

In several studies, the advantage of RT was observed in patients with advanced NSCLC and EGFR-mutation. For instance, Qiu B *et al*¹⁵ reported that 46 patients with stage IIIB/IV EGFR-mutated NSCLC were treated with local therapy (mainly RT) and continued TKIs for oligoprogression. The 2-year and estimated median OS were 65.2% and 35 months, respectively. Yen YC *et al*⁸ proposed that thoracic RT might improve OS in patients exhibiting stages IIIB to IV unresectable lung adenocarcinomas with EGFR mutation and in patients receiving EGFR-TKI treatment in response to the clinical condition. In the study by Hu F *et al*,⁷ combinational therapy, including EGFR-TKIs, and local consolidated therapy (LCT), showed significant benefits and improved PFS (15 vs 10 months, $P < .001$) and OS (34 vs 21 months, $P = .001$) in comparison with EGFR-TKI treatment alone for EGFR mutation-positive oligometastatic lung adenocarcinoma patients. Interim results of SINDAS indicated that TKIs with

Table 2. The Overall Survival (OS) and Progression-free Survival (PFS) Under Univariate Analysis.

Factors	Groups	Cases	Median OS	<i>P Value</i>	Median PFS1	<i>P Value</i>	Median PFS2	<i>P Value</i>
Gender	Male	101	30.2(24.3-36.2)	.338	12.3(9.4-15.2)	.408	24.9(18.9-30.9)	.946
	Female	137	31.6(24.4-38.8)		15.2(13.0-17.4)		26.4(20.8-32.0)	
Age	≤65	115	34.0(29.8-38.3)	.042	14.6(12.5-16.6)	.823	26.4(20.8-32.0)	.399
	>65	134	24.9(20.1-29.9)		13.1(9.9-16.3)		21.5(17.2-25.8)	
Clinical Stage	III	33	22.8(8.7-36.9)	.031	13.2(8.1-18.3)	.206	19.2(2.4-36.0)	.090
	IVA	84	34.8(26.6-43.1)		15.2(12.0-18.4)		30.2(22.9-37.6)	
	IVB	121	27.4(22.8-32.1)		12.3(9.6-15.0)		21.3(15.3-27.3)	
EGFR Mutations	19-deletion	94	34.1(30.2-38.0)	.235	14.1(12.5-15.9)	.806	27.4(17.3-37.4)	.945
	21-mutation	118	28.1(20.4-35.7)		14.6(11.7-17.4)		25.6(19.9-31.3)	
	Others	26	21.3(19.6-23.0)		7.1(3.5-10.8)		20.3(5.5-35.0)	
Sequence of TKI and CT	TKI alone	120	27.4(19.3-35.5)	.078	16.1(13.0-19.1)	.042	23.4(17.4-29.3)	.129
	TKI + ConCT	43	28.1(18.0-38.1)		12.1(6.4-17.8)		24.9(17.8-32.0)	
	TKI + seqCT	32	32.5(23.0-42.1)		11.0(6.6-15.5)		18.5(14.0-23.0)	
	CT seqTKI	43	44.3(30.7-58.0)		13.5(9.6-17.4)		40.0(29.9-51.1)	
Type of TKIs	Gefitinib	89	32.4(24.1-40.7)	.883	14.2(10.9-17.5)	.323	28.1(18.0-38.1)	.060
	Icotinib	109	30.3(24.5-36.1)		13.8(10.0-17.6)		27.7(20.8-34.1)	
	Erlotinib	29	30.2(18.9-41.5)		14.7(9.8-19.7)		22.0(14.4-29.7)	
	others	11	21.5(16.1-26.8)		10.3(-21.3)		12.0(-24.8)	
Site of RT	Primary tumor	76	34.1(25.0-43.2)	.309	14.7(11.0-18.5)	.197	33.3(23.0-43.6)	.222
	Brain	100	29.8 (24.4-35.2)		14.6(11.1-18.1)		26.5(20.2-32.8)	
	Bone	42	30.2 (20.2-40.2)		11.0(6.8-15.1)		22.0(14.6-29.5)	
	Two sites	20	25.4(10.36-40.4)		13.5(10.8-16.3)		16.9(12.2-21.6)	
Timing of RT	Non-PD	101	30.2(24.3-36.2)	.338	16.8(10.4-23.2)	.041	28.8(15.8-41.8)	.669
	PD	137	31.6 (24.4-38.8)		13.2(11.1-15.3)		24.9(20.1-29.7)	
Dose of RT	<50Gy	111	30.2(23.3-37.3)	.208	12.3(10.3-12.3)	.026	24.9(19.7-30.0)	.160
	≥50Gy	127	30.3(25.2-35.5)		15.5(12.3-18.8)		28.8(18.4-38.2)	
Total response	CR + PR	114	32.5(25.1-39.9)	.101	18.2(14.4-22.1)	.000	32.5(25.2-39.8)	.001
	SD	70	27.2(18.5-35.8)		11.7(9.5-13.9)		18.7(19.9-23.5)	
	PD	54	33.3(22.0-44.6)		10.9(7.7-14.1)		18.7(14.3-23.1)	

Abbreviations: CT, chemotherapy; Con, concurrent; EGFR, epidermal growth factor receptor; RT, radiotherapy; seq, sequence; PFS1, progression-free survival 1; PFS2, progression-free survival 2; TKI, tyrosine kinase inhibitor.

upfront local radiation therapy could significantly increase median OS (from 17.4 to 25.5 months, $P < .001$) and PFS (from 12.5 to 20.2 months, $P < .001$), when compared with TKIs alone for patients with EGFR, mutated oligometastatic NSCLC.¹⁰ Hu F *et al*¹⁶ reported that a combination treatment of TKIs with local consolidative therapy (LCT, $n = 62$) demonstrated a longer OS (36.3 vs 21.0 months, $P = .01$) and PFS (14.0 vs 8.1 months; $P = .01$), which conferred a greater statistical significance over the monotherapy group ($n = 65$) in patients with EGFR mutation-positive bone oligometastatic lung adenocarcinoma. Xu Q *et al*¹⁷ suggested that a consolidative local ablative therapy (LAT, combining RT and surgery or applying each independently) could significantly improve PFS and OS for stage IV EGFR-mutant NSCLC patients who were treated with first-line EGFR-TKIs. The mPFS and mean OS were 20.6 and 40.9 months in the all-LAT group, 15.6 and 34.1 months in part-LAT, and 13.9 and 30.8 months in non-LAT, respectively, conferring a statistical significance ($P < .001$).

A retrospective multicenter study by Bi N *et al*⁹ showed that first-line TKI combined with RT could remarkably improve the PFS (21.6 months) when compared with CRT alone (12.6 months) or upfront TKI (16.5 months, $P < .001$) in 367 patients

with local unresectable EGFR-mutant and advanced NSCLC. Results reveal that TKI combined with RT dramatically increased the OS compared with upfront TKI (67.4 vs 46.5 months, $P < .001$). Accordingly, the median OS and PFS1 were 30.3 and 14.1 months, and the 1-, 3-year OS and 1-, 3-year PFS1 were 84.4%, 38.7%, and 57.0%, 15.7%, respectively. While survival rate following TKI treatment and local therapy was similar to previous studies,^{7,8,15-17} it increased after combined treatment compared to TKI alone in patients with EGFR-mutated advanced NSCLC.

EGFR mutation might probably associate with prognosis. In a meta-analysis, Qin Q *et al*¹⁸ found that EGFR-mutant patients with locally advanced unresectable stage III NSCLC after definitive chemoradiotherapy (CRT) had a significantly lower local, regional recurrence, higher distant progression, and higher brain metastasis when compared to patients with wild-type EGFR. However, an insignificant difference was found in the overall response rate (ORR), PD, PFS, and OS. Park SE *et al*¹⁹ reported that EGFR mutation led to a significantly lower ORR (72.2% for vs 93.8%, $P < .001$) and shorter PFS (8.9 vs 11.8 months, $P = .013$) when compared with wild type EGFR in 197 patients with stage III non-squamous NSCLC after definitive CRT. Tanaka K *et al*²⁰ found that

Table 3. The overall survival (OS) and progression-free survival (PFS) under multivariate analysis.

Factors		Group	HR (95% CI)	P Value
OS	Age	>60	1.447 (1.021-2.050)	.038
	Clinical Stage	IVB		.005
		III	0.783 (0.457-1.342)	.374
		IVA	0.535 (0.365-0.785)	.001
		CT seq		.042
	Sequence of TKI and CT	TKI alone	1.974 (1.203-3.238)	.007
		TKI + con CT	1.781 (0.989-3.206)	.054
		TKI + seq CT	1.717 (0.950-3.103)	.074
	Total response	CR + PR		.014
		SD	1.834 (1.229-2.739)	.003
PD		1.365 (0.877-2.124)	.169	
PFS1	Clinical Stage	IVB	0.642 (0.465-0.886)	.007
		III	0.639 (0.403-1.015)	.058
		IVA		
	Total response	CR + PR		<.001
		SD	2.186 (1.537-3.108)	<.001
PFS2	Clinical Stage	IVB		.004
		III	0.650 (0.374-1.133)	.128
		IVA	0.545 (0.375-0.791)	.001
		others		.011
	Type of TKIs	Gefitinib		.075
		Icotinib	1.003 (0.697-1.442)	.989
		Erlotinib	1.357 (0.835-2.204)	.218
		others	2.779 (1.263-6.113)	.011
	Sequence of TKI and CT	CT seq		.033
		TKI		
		TKI	1.946 (1.211-3.129)	.006
		TKI con CT	1.792 (1.014-3.169)	.045
		TKI seq CT	1.815 (1.028-3.206)	.040
	Total response	CR + PR		<.001
		SD	2.213 (1.497-3.270)	<.001
PD		1.961 (1.274-3.017)	.002	

Abbreviations: CT, chemotherapy; HR, hazard ratio; seq, sequence; PD, disease progression; PFS1, progression-free survival 1; PFS2, progression-free survival 2; TKI, tyrosine kinase inhibitor.

EGFR-mutant patients with locally advanced stage III NSCLC after concurrent CRT had a significantly shorter PFS (9.8 vs 16.5 months, $P=.041$), 2-year recurrence-free survival rate (7.7% vs 28.1%, $P=.028$), more frequently distant metastases (76% vs 40%, $P=.001$), and less common locoregional recurrence (14% vs 35%, $P=.027$) in compared with EGFR-mutant patients. Park S et al²¹ proposed that exon 19 deletion (19-Del) and exon 21 L858R (21-L858R) mutation are strongly associated with superior PFS and OS compared with uncommon mutations in EGFR-mutant lung adenocarcinoma patients. The median PFS and OS were 14.7 and 38.6 months for 19-Del, 10.9 and 28.6 months for 21-L858R mutation, and 5.0 and 22.8 months for uncommon mutations ($P < .01$), respectively. Xu Q et al¹⁷ reported an association

of 19-Del with longer OS and PFS than exon 21 mutation in patients with synchronous oligometastatic NSCLC after first-line TKIs and consolidative local ablative therapy. In a study by Zhou X et al,²² the survival time of patients with lung adenocarcinoma and EGFR mutations, or 19-Del, increased compared to patients without EGFR mutations or 19-Del. However, an insignificant difference in OS was observed between patients with or without the 21-L858R mutation or with or without other mutations of EGFR. Several studies confirm that advanced NSCLC patients with 19-Del had significantly longer median PFS,^{23,24} and OS.²⁴ In contrast, Hu F et al¹⁶ reported that EGFR mutation status (19-Del/21-L858R/others) was not associated with OS and PFS in patients with EGFR mutation-positive bone oligometastatic lung adenocarcinoma who received TKIs and local consolidative therapy. Hu F et al⁷ suggested that EGFR mutation status (19-Del/21-L858R/others) had no association with OS and PFS in oligometastatic lung adenocarcinoma patients who received first-line TKIs and local consolidative therapy. Our results are by those of Hu F et al,^{7,16} which reveals that the status of EGFR mutation (exon 19 vs exon 21 vs other mutation) does not confer any association with OS, PFS1, or PFS2 in stage IV lung cancer adenocarcinoma patients who receive the TKI and RT regime. It is uncertain that our study's results differed from previous studies.¹⁷⁻²⁴ this should be further explored in the future.

The administration of TKIs in patients with EGFR mutant NSCLC might be associated with the survival rate. Huang MY et al¹⁴ reported that the median OS and PFS were similar in patients with advanced lung adenocarcinoma harboring EGFR mutation after being treated with gefitinib and erlotinib. Park S et al²¹ proposed that the median PFS duration periods for erlotinib and gefitinib are 11.2 and 10.9 months, respectively. Moreover, administration of erlotinib for patients with L858R demonstrated a significantly inferior OS compared with other TKIs (30.8 months for erlotinib vs 48.4 months for gefitinib; $P < .05$). Following treatment with gefitinib, a significant inferior PFS (4.6 in gefitinib vs 10.6 months in erlotinib; $P < .05$) was similarly observed in patients with uncommon mutations. Based on the above reports, our study found that OS and PFS1 are similar for different types of TKIs in patients with advanced lung adenocarcinoma harboring EGFR mutation; yet, low PFS2 was observed in patients who received TKIs other than gefitinib.

Combined treatment is related to improved survival of patients with EGFR mutant NSCLC. Zhang Y et al²⁵ suggests that the first-line icotinib combined with CT can significantly increase ORR (79.3% vs 52.1%; $P < .001$), PFS (16.9 vs 9.9 months; $P < .001$), PFS2 (16.9 vs 14.1 months; $P=.009$), and OS (33.2 vs 26.5 months; $P < .001$) compared to first-line icotinib alone in patients with advanced NSCLC with sensitive EGFR mutations. Liu Y et al²⁶ indicated that administration of TKI combined with RT in brain metastasis significantly improved the intracranial ORR (84.4% vs 63.2%, $P < .01$) and DCR (97.4% vs 80.7%, $P < .01$). In addition, the researchers found the combined treatment to be significantly associated with longer iPFS ($P < .001$), systematic PFS ($P=.007$), and OS

($P = .018$) compared with TKI alone in patients with advanced lung adenocarcinoma and brain metastasis carrying EGFR sensitive mutations. The results further demonstrated that EGFR Del-19 is associated with improved OS. Li C et al²⁷ reported an upfront WBRT, which can significantly improve ORR and OS in patients with EGFR-mutant lung adenocarcinoma and multiple brain metastases (BM). The ORR values of the upfront WBRT group, concurrent group, and upfront TKI group were 82%, 64%, and 63% ($P = .004$), while OS values were 36, 25, and 25 months ($P < .0001$), respectively, with a statistical significance. Another meta-analysis report on 24 studies, including 2810 patients, showed that RT with EGFR-TKIs resulted in higher ORR and DCR and longer OS and I-PFS than monotherapy, although with higher overall AEs (20.2% vs 11.8%).²⁸ Our multivariate analysis revealed that CT seq TKI could significantly improve PFS2 compared with TKI alone, TKI con CT, and TKI seq CT. CT seq TKI could significantly improve OS compared to TKI alone and tended to increase OS compared with TKI con CT and TKI seq CT. Moreover, these results should be further verified in a larger sample size.

Determining the clinical stages of NSCLC patients is critical for improving their survival. Our results showed that OS, PFS1, and PFS2 were longer in stage IVA than in stage IVB but were not significantly different between stage III and staged IVA or IVB. Concomitant CT is still considered the standard method for unresectable stage III NSCLC; thus, first-line TKI treatment is probably not optimal for patients with stage III NSCLC with EGFR mutation.

In our study, the total response was also an independent factor of OS, PFS1, and PFS2 in patients with advanced EGFR mutant lung adenocarcinoma. Accordingly, OS, PFS1, and PFS2 were longer in patients with CR + PR than in patients with SD or PD. We also found that the total response was related to the clinical stage and the sequence of TKI and CT, while ORR was lower in patients with stage III than those with stage IVA and IVB. Comparatively, ORR was higher in patients who received TKI alone than those administered with TKI combined with CT. This may be because patients who demonstrated improvement after the first-line TKI treatment chose to continue TKI alone, while those who experienced PD after first-line TKI treatment selected combination CT. Although ORR was higher in patients with TKI alone, the survival was higher in patients who received TKI combined with CT, especially CT and sequence TKI.

Despite promising results, this study has several limitations. First, this is a retrospective study, so selection bias could not be avoided. Second, 3 different first-line TKIs were used; however, the survival was similar among other TKIs. Third, the timing, regimes, and cycles of CT were inconsistent, which may have affected the survival rate. Fourth, the site of RT was recommended only for the primary tumor, metastasis tumor of brain or bone, most of the patients accepted RT after PD, and the dose and timing of RT were varied, which may have influenced the survival rate such as PFS even OS. Moreover, RT in non-PD patients and the amounts of RT

greater than 50 Gy were associated with longer PFS1 in this study.

In conclusion, the side effect during RT is tolerable, and the total response is also for patients with advanced lung adenocarcinoma exhibiting EGFR mutation that received EGFR-TKIs. Sequential CT with TKIs is most likely associated with longer OS and PFS, while the treatment response of CR + PR may be related to a longer duration of OS, PFS1, and PFS2. However, further study is required in a larger sample size to confirm the results.

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Ethical Approval

Ethical approval to report this case series was obtained from the Ethics Committee of the Fourth Hospital of Hebei Medical University (approval number : 2021KY253). Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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