Journal of Biosciences and Medicines, 2024, 12, 142-154
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Efficacy and Safety of Primary Radiotherapy in Combination with EGFR-TKIs for Non-Small Cell Lung Cancer Harboring EGFR Mutation

Dongxu Ao[1*], Meng Wang[1], Jinyuan Xie[2], Yang Zhang[1], Xinran Zhang[1], Ya Shu[1], Chenshi Lin[1], Qingqing Ye[3#]

[1]Department of Oncology, The First Affiliated Hospital of Yangtze University, Jingzhou, China
[2]Department of Joint Surgery and Sports Medicine, Jingmen Central Hospital, Jingmen, China
[3]Department of Breast Surgery, The First Affiliated Hospital of Yangtze University, Jingzhou, China
Email: #zhiyin0540@163.com

How to cite this paper: Ao, D.X., Wang, M., Xie, J.Y., Zhang, Y., Zhang, X.R., Shu, Y., Lin, C.S. and Ye, Q.Q. (2024) Efficacy and Safety of Primary Radiotherapy in Combination with EGFR-TKIs for Non-Small Cell Lung Cancer Harboring EGFR Mutation. *Journal of Biosciences and Medicines*, **12**, 142-154.
https://doi.org/10.4236/jbm.2024.129014

Received: May 27, 2024
Accepted: September 16, 2024
Published: September 19, 2024

Abstract

Objective: To evaluate the efficacy and safety of EGFR-TKI with the radiotherapy in EGFR mutant metastatic NSCLC. **Methods:** Retrospective analysis of 72 patients with stage IV lung cancer with EGFR-sensitive mutation. Patients in the A group were treated with the first-generation EGFR-TKI (Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor) combined with radiotherapy for primary tumors (34 cases). The B group was treated with the first-generation EGFR-TKI alone until the disease progressed (38 cases). PFS, OS, pulmonary infection and hematological toxicity during treatment were commented in both groups. **Results:** The objective remission rate was 47.1% (16/34) in the A group and 21.1% (8/38) in the B group. There was a significant difference between the two groups. There was no significant difference in hematological toxicity between the A group and the B group. There were 10 patients (29.4%) with degree II pulmonary infection in the A group and 3 patients (7.9%) in the B group. The difference between the two groups was statistically significant, suggesting that the incidence of pneumonia in the A group was higher than that in the B group. The median PFS (Progression-Free Survival)) and OS (Overall Survival) of the A group were significantly longer than those of the B group (16.5 months vs 9 months) and the median OS (36 months vs 19 months). The PFS and OS in the A group were significantly longer than those in the B group. **Conclusion:** EGFR-TKI combined with primary radiotherapy can significantly prolong the drug resistance time of EGFR mutant metastatic NSCLC.

*First author.
#Corresponding author.

Keywords

Non-Small Cell Lung Cancer, Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor, Radiotherapy

1. Introduction

Previous studies have shown that for patients with advanced non-small cell lung cancer with EGFR gene-sensitive mutation, EGFR-TKI (including gefitinib, erlotinib, etinib, etc.) is significantly superior to traditional chemotherapy in the treatment of advanced NSCLC [1]-[10]. The progression-free survival of the patients can reach 9.6 months to 13.1 months, and the adverse reactions of EGFR-TKI treatment are even lighter. The patient has better tolerance. However, in clinical work, we have observed that after 2 - 3 months of treatment with EGFR-TKI, the primary tumor in the lung of most patients will not continue to shrink, to be stable until the disease progresses. At this time, does the local radiotherapy of the primary lung tumor prolong the patient's resistance time and strive for a longer survival period? A randomized controlled trial [11] in 2016 showed first-line treatment for advanced lung cancer (including in patients who did not progress after platinum-containing chemotherapy or EGFR-TKI/ALK-TKI treatment) combined with local treatment (radical radiotherapy or surgery), the patient's PSF was nearly three times longer than simple maintenance therapy (11.9 months vs 3.9 months). Blake-Cerda's study [12] also showed that after first-line chemotherapy for patients with advanced lung cancer without an EGFR-TKI or ALK-TKI-sensitive mutation, the combination of chemotherapy and stereotactic radiotherapy is better than that of chemotherapy alone. Control time was extended from 3.5 months to 9.7 months. The study by Li *et al*. [13] suggested that combination therapy is mentioned as a new strategy to overcome or at least delay the emergence of acquired resistance to third-generation EGFR TKIs in non-small cell lung cancer (NSCLC), where radiotherapy can restore sensitivity to TKIs in resistant metastatic disease and improve survival outcomes. In this study, patients who were effective after treatment with EGFR-TKI were selected to determine whether EGFR-TKI combined with primary pulmonary radiotherapy could prolong the drug resistance time compared with the simple EGFR-TKI treatment group and evaluate its safety.

2. Materials and Methods

2.1. Patients

A retrospective study was conducted on 72 patients with stage IV EGFR-mutant (19 exon deletion or 21 exon l858 mutation) NSCLC who had diagnosis from January 2014 to December 2016 at First Affiliated Hospital of Yangtz University. All patients with ECOG ≤ 2 points, including combined radiotherapy group (34 cases) and simple targeted treatment group (38 cases). Among the 72 patients, 35

were male and 37 were female. Age distribution ranges from 46 to 77 years, with a median age of 65 years. Among the patients, there were 29 cases with a history of smoking and 43 cases without a history of smoking. There were 40 patients with exon 19 deletion mutations and 32 patients with exon 21 L858R mutations (Table 1).

Table 1. Distribution of smoking history and gene mutation types.

Smoking history	Total number (N = 72)
Smoker	29
Non-smoker	43
Gene mutation types	**Total number (N = 72)**
Exon 19 deletion	40
Exon 21 L858R mutation	32

2.2. Method

Patients treated with first-line TKI (One of the following: Erlotinib 150 mg/day, Gefitinib 250 mg/day, or Alectinib 375 mg/day.) without progression followed by primary tumor radiation were identified (TKI plus RT group). Patients who received radiation at the time of progression were not included in the TKI plus RT group. Conformal intensity modulation radiotherapy guided by CT image, body network fixation, CT simulated localization, American Warian linear accelerator, 6MV-X line irradiation and primary lung tumor dose 50 - 66 Gy (2 Gy/times, 5 times per week) were used for radiotherapy. EGFR-TKI continued to be treated by oral administration during radiotherapy until the disease progressed or there were intolerable adverse reactions. The curative effect of radiotherapy was evaluated 1 month after radiotherapy. Patients with stage IV EGFR mutant NSCLC treated with first-line TKI were identified (TKI-only group). TKI-only group was treated with EGFR-TKI for one-month evaluation of efficacy and continued oral EGFR-TKI treatment until disease progression or an intolerable adverse reaction occurred.

2.3. Evaluation Criteria

Evaluation of therapeutic effect according to solid tumor efficacy evaluation criteria (RECIST 1.1). Complete remission (CR) was defined as the disappearance of all known lesions. Partial remission (PR) was defined as a decrease of 30% or greater in the sum of the longest diameters of the target lesions from baseline. Stable disease (SD) was defined as an insufficient decrease in size in tumor to qualify for PR or an insufficient increase in size to qualify for PD. Progressive disease (PD) was defined as at least 20% increase in the sum of the longest diameters of the target lesions or the appearance of new lesions.

1) Objective remission rate (ORR) = CR + PR/total number of cases × 100%, Disease control rate (DCR) = CR + PR + SD/total number of cases × 100%. 2) Adverse reaction classification: According to the WHO classification criteria, ① The

hematological toxicity reaction is classified as follows: Grade 0 is WBC > 4.0 × 10^9/L, Grade 1 is 3.0 - 3.9 × 10^9/L, Grade 2 is 2.0 - 2.9 × 10^9/L, Grade 3 is 1.0 - 1.9 × 10^9/L, and Grade 4 is <1.0 × 10^9/L. Grade 0 is platelet ≥ 100 × 10^9/L, Grade 1 is 75 - 99 × 10^9/L, Grade 2 is 50 - 74 × 10^9/L, Grade 3 is 25 - 49 × 10^9/L, Grade 4 is platelet < 25 × 10^9/L. Grade 0 is Hb ≥ 110 g/L, Grade 1 is 95 - 109 g/L, Grade 2 is 80 - 94 g/L, Grade 3 is 65 - 79 g/L, and Grade 4 is <65 g/L. ② Classification of pulmonary infections was based on the grading standard of radiation pneumonia in the American Tumor Radiotherapy Cooperative Group and the European Tumor Therapy Research Cooperation Group (RTOG/EORTC). Grade 0: no change; Grade 1: mild dry cough or exertional dyspnea; Grade 2: sustained cough requires an anesthetic antitussive, mild dyspnea, but no difficulty breathing at rest; Grade 3: severe cough There is no relief of narcotic antitussives, and there are clinical manifestations or radiographic changes of acute pneumonia with dyspnea at rest. Intermittent oxygen or hormonal therapy is required. Grade 4: severe dyspnea requires continuous oxygen inhalation.

2.4. Observation Indicators

The adverse events of patients in TKI plus RT group and TKI-only group were recorded. Evaluation of pulmonary CT in TKI plus RT group 1 month after radiotherapy. CT was reviewed after 1 month of oral TKI in the TKI-only group. The PFS and OS of the patients in the two groups were followed up. The deadline for follow-up is January 31, 2019. The follow-up included physical examination, blood routine, blood biochemical test, head MRI, chest and abdomen CT, systemic bone scan.

2.5. Statistical Methods

The data were processed by SPSS 20.0 statistical software. Survival curves were plotted using Kaplan-Meier survival analysis and compared by log-rank test. The chi-square test was used to compare between groups. Relative risks (RRs) of death were estimated using unvaried Cox proportional hazards model. In the current analyses, a RR of 1.000 was set as a baseline for factors including age (<65 years), Male, lack of smoking, Exon 19 deletion, T1 + T2, N0 + N1 and treat with TKI only. Progression-free time (PFS) refers to the period of time between the onset of treatment to the onset of disease progression, or the death of any cause. Overall survival (OS) was defined as the period from the date of the time from treatment commencement of EGFR-TKI to the date of death. $p < 0.05$ was considered statistically significant.

3. Result

3.1. Efficacy Evaluation and Adverse Reactions

There were no statistically significant differences in age, gender, smoking history, EGFR mutation, T-stage and N-stage between the TKI plus RT group and the TKI-only group. Among the 34 patients in the TKI plus RT group, 16 patients (47.1%)

had CR/PR, 17 patients (50%) had SD, and 1 patient (2.9%) had PD; the ORR was 47.1% (16/34). Among the 38 patients in the TKI-only group, 8 patients (21.1%) had CR/PR, 24 patients (63.1%) had SD, and 6 patients (15.8%) had PD; the ORR was 21.1% (8/38). The difference between the two groups was statistically significant (p = 0.022) (Table 2).

There were 3 cases (8.8%) with no myelosuppression in 34 patients in the TKI plus RT group, 14 cases (41.2%) with Grade 1 myelosuppression, and 13 cases (38.2%) with Grade 2 myelosuppression; 4 patients (11.8%) with Grade 3 myelosuppression; 7 patients (18.4%) had no myelosuppression in 38 patients in the TKI-only group, and 20 patients (52.6%) had Grade 1 myelosuppression. There were 10 cases (26.3%) with Grade 2 myelosuppression, and 1 case (2.6%) with Grade 3 myelosuppression; there was no significant difference between the two groups (p = 0.186) (Table 2).

Of the 34 patients in the TKI plus RT group, 8 (23.5%) had no pulmonary infection, 16 (47.1%) had degree I pulmonary infection and 10 (29.4%) had degree II pulmonary infection, 22 (57.9%) had no pulmonary infection, Of the 38 patients in the TKI-only group, 22 (57.9%) had no pulmonary infection, 13 (34.2%) had degree I pulmonary infection and 3 (7.9%) had degree II pulmonary infection, There was significant difference between the two groups (p ≤ 0.005) (Table 2).

Table 2. Patients' characteristics.

Characteristics	R + TKI (34)	TKI (38)	p
	No. (%)	No. (%)	
Age (y)			
<65	16 (47.1)	17 (44.7)	0.844
≥65	18 (52.9)	21 (55.3)	
Gender			
Male	18 (52.9)	17 (44.7)	0.487
Female	16 (47.1)	21 (55.3)	
Smoking status			
No	20 (58.8)	23 (60.5)	0.883
Yes	14 (41.2)	15 (39.5)	
EGFR mutation			
Exon 19 deletion	20 (58.8)	20 (52.6)	0.598
Exon 21 L858R	14 (41.2)	18 (47.4)	
T stage			
T1-2	15 (44.1)	16 (42.1)	0.863
T3-4	19 (55.9)	22 (57.9)	
N stage			
N0-1	5 (14.7)	6 (15.8)	0.898
N2-3	29 (85.3)	32 (84.2)	

Continued

Myelosuppression			
0	3 (8.8)	7 (18.4)	0.186
1	14 (41.2)	20 (52.6)	
2	13 (38.2)	10 (26.3)	
3	4 (11.8)	1 (2.6)	
Pulmonary infection			
0	8 (23.5)	22 (57.9)	0.005
1	16 (47.1)	13 (34.2)	
2	10 (29.4)	3 (7.9)	
Evaluation			
CR/PR	16 (47.1)	8 (21.1)	0.022
SD	17 (50.0)	24 (63.1)	
PD	1 (2.9)	6 (15.8)	

3.2. Survival Analysis

The median PFS of the patients in the TKI plus RT group was 16.5 months in Table 2, and the median PFS of the patients in the TKI-only group was 9 months. Combined with local radiotherapy, it extended the progression-free survival time of 7.5 months. The difference was statistically significant. The median OS of the patients in the TKI plus RT group was 36 months; the median OS of the patients in the TKI-only group was 19 months, suggesting that combined radiotherapy can significantly prolong the survival time of the patients, and the difference between the two groups is statistically significant (Table 2).

The relative risk of death was compared using the Cox proportional hazards model. From Figure 1, we can see that EGFR-TKI combined radiotherapy can significantly reduce the risk of death in patients with EGFE mutation NSCLC compared with radiotherapy alone, and the difference is statistically significant ($p \leq 0.007$). Higher T stage (T1/T2 vs T3/T4) suggests a relatively poor prognosis ($p \leq 0.043$). When the patient's age, gender, smoking history, EGFR mutation type and N stage were independent factors, there was no significant difference in the relative risk of death.

The results of this study indicate that combined radiotherapy significantly prolongs progression-free survival (PFS) and overall survival (OS) in patients with EGFR-mutant advanced non-small cell lung cancer (Table 3), which is consistent with the findings of Faehling *et al*. This study pointed out that local treatment after effective systemic therapy can significantly extend PFS (11.9 months compared to 3.9 months) [14]. Additionally, a retrospective analysis by Yasir Elamin also showed that patients with EGFR-TKI sensitive mutations who received targeted therapy combined with local treatment had a PFS of up to 36 months, much higher than the 14 months in the targeted therapy alone group [15]. These studies

collectively support the importance of combined radiotherapy in delaying resistance to targeted therapy.

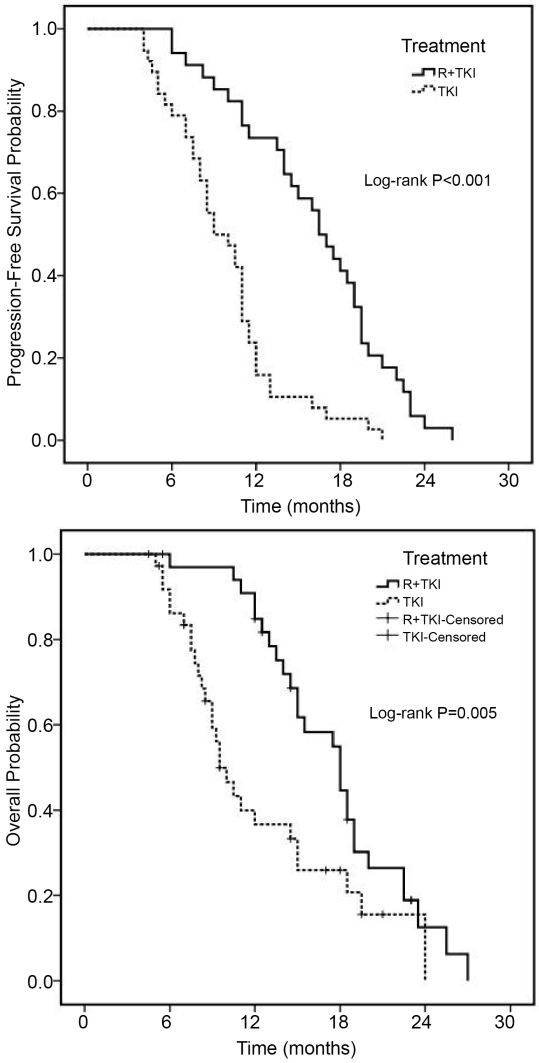

Figure 1. Comparison of combination therapy (R + TKI) and single TKI therapy in progression-free and overall survival.

Table 3. Univariable analysis of covariables associated with OS.

Characteristics	Univariable analysis		
	HR	95%CI	p
Age (y)			
<65	1.00		0.681
≥65	1.12	0.65 - 1.93	
Gender			
Male	1.00		0.969
Female	1.01	0.59 - 1.74	

Continued

Smoking status			
No	1.00		0.748
Yes	1.10	0.63 - 1.89	
EGFR mutation			
Exon 19 deletion	1.00		0.929
Exon 21 L858R	0.97	0.55 - 1.73	
T stage			
T1-2	1.00		0.043
T3-4	1.78	1.02 - 3.11	
N stage			
N0-1	1.00		0.500
N2-3	0.78	0.38 - 1.61	
Treatment			
TKI	1.00		0.007
R + TKI	0.46	0.27 - 0.81	

The findings of this study further validate the potential mechanisms of combining EGFR-TKI with radiotherapy, including that EGFR-TKI may enhance the effects of radiotherapy by causing cell cycle arrest and promoting tumor cell apoptosis, which aligns with existing literature on the theory of EGFR-TKI enhancing radiotherapy sensitivity [16]. Therefore, this study not only provides new insights into the treatment of advanced non-small cell lung cancer with EGFR mutations but also lays the groundwork for future clinical trials, emphasizing the potential value of combined treatment strategies in improving patient outcomes.

4. Discussion

Lung cancer is the leading malignant tumor in China in terms of both mortality and incidence rate. Most patients are diagnosed at an advanced stage [17], losing the chance for surgery. Historically, systemic chemotherapy was the primary treatment for patients with advanced lung cancer. However, in the past decade, the discovery of targeted genes has provided new hope for lung cancer patients. Clinically identified lung cancer driver genes include mutations such as EGFR, ALK, BRAF, KRAS, and HER2. In Asian lung adenocarcinoma patients, 87% have detectable known driver genes, and 66% of these driver genes have explicit targeted inhibitors [18]. The EGFR gene was the first lung cancer driver gene to be systematically studied, with a mutation probability of about 50% among Asian lung adenocarcinoma patients [19]. First-generation EGFR-TKIs include gefitinib, erlotinib, and icotinib, with multiple clinical studies (IPASS, WJTOG 3405, NEJ002, OPTIMAL, First-SIGNAL, EURTAC, ENSURE) showing that first-line EGFR-TKI treatment significantly outperforms traditional chemotherapy, with progression-free survival

(PFS) ranging from 9.6 months to 13.1 months and milder adverse reactions. The CTONG0901, ICOGEN, and WJOG5108L studies compared the efficacies of three first-generation EGFR-TKIs, showing comparable efficacy among patients with EGFR mutation-positive lung cancer in first-line treatment. After about 10 months of first-generation EGFR-TKI treatment, patients often develop acquired resistance, with T790M as a major molecular mechanism. Second-generation EGFR-TKIs have limited effectiveness in overcoming T790M resistance, leading to the emergence of third-generation EGFR-TKIs such as osimertinib (Osimeritinib, AZD9291), CO-1686, and HM61713, among which osimertinib is currently the only FDA-approved third-generation EGFR-TKI. The FLAURA study shows that osimertinib significantly extends median PFS to 18.9 months compared to standard first-line therap [20]. Osimertinib can cross the blood-brain barrier, providing better treatment for patients with brain metastases. However, resistance to third-generation EGFR-TKIs remains inevitable over time, making prolonging resistance time a focal point of clinical research. This study mainly compares the PFS, OS, and adverse reactions of patients effective on first-generation EGFR-TKI treated with primary tumor local radiotherapy versus simple targeted maintenance, aiming to determine whether the combination radiotherapy group can significantly extend the resistance time of targeted therapy compared to the simple EGFR-TKI treatment group and assess its safety.

As early as 2006, Das *et al*. conducted foundational research on the radiosensitivity of non-small cell lung cancer cells with EGFR mutations. The study showed that EGFR-mutant cell lines, including T790M mutations resistant to first-generation EGFR-TKIs, are sensitive to radiotherapy, whereas wild-type cells resist it, suggesting a radiosensitizing effect of EGFR-TKIs. The mechanisms mainly include: 1) EGFR-TKIs can cause cell cycle arrest, increasing the proportion of tumor cells in the radiation-sensitive G0/G1 phase, thereby enhancing radiosensitivity [21] [22]; 2) EGFR-TKIs promote tumor cell apoptosis, reducing tumor burden while inhibiting radiation-induced EGFR autophosphorylation and blocking downstream EGFR signaling pathways, thus reducing radiation resistance [22]-[24]; 3) EGFR-TKIs inhibit DNA double-strand break repair, particularly the early stages of this process, hindering the repair of radiation damage [25]-[27]; 4) Several preclinical studies show that EGFR-TKIs promote vascular normalization, improving hypoxic conditions and further increasing radiotherapy sensitivity [28] [29]. In summary, radiation directly targets local lesions treated with EGFR-TKIs, killing tumor cells and shrinking local lesions. Meanwhile, EGFR-TKIs increase sensitivity and effectiveness of local tumor radiotherapy, maintaining effective control over other systemic lesions.

The clinical study by Lemine Sow *et al*. shows that, for patients with advanced non-small cell lung cancer with distant metastasis who responded to systemic treatments (chemotherapy or EGFR-TKI/ALK-TKI), combining local treatment modalities, such as local radiotherapy or surgery, with systemic therapy significantly extends PFS (11.9 months vs 3.9 months) [30] compared to maintenance

chemotherapy or targeted therapy alone. A retrospective analysis reported by Yasir Elamin found that in 12 patients with sensitivity to EGFR-TKIs who received targeted therapy followed by local treatments (11 received radiation therapy and 1 underwent surgery), the PFS reached 36 months, significantly higher than the 14 months in the targeted therapy alone group, with a statistically significant difference. Ma e*t al*.'s research [31] further shows that median PFS for the completely loco-regionally treated group, partially loco-regionally treated group, and untreated group after targeted therapy were 20.6 months, 15.6 months, and 13.9 months, respectively, with median OS being 40.9 months, 34.1 months, and 30.8 months ($p < 0.001$). The completely treated group's median PFS and OS were extended by 6.7 months and 10.1 months [32] respectively, compared to the untreated group. Although these studies highlight the significance of combining local radiotherapy in delaying resistance to targeted therapy in advanced lung cancer, limitations include small sample sizes, unclear EGFR mutation statuses, lack of intergroup comparisons, or lack of pre-and post-treatment comparisons.

The results of this study show that the objective response rate in the combined radiotherapy group was 47.1%, significantly higher than the 21.1% in the targeted therapy alone group. Additionally, the median progression-free survival (PFS) in the combined radiotherapy group was 16.5 months, significantly greater than the 9 months in the targeted therapy alone group. Meanwhile, the median overall survival (OS) in the combined radiotherapy group was 36 months, significantly higher than the 19 months in the targeted therapy alone group. These results indicate that combined radiotherapy not only effectively increases the response rate in patients but also significantly prolongs survival time, with all comparisons showing statistical significance ($p < 0.05$). However, the incidence of Grade 2 pulmonary infections in the combined radiotherapy group was 29.4%, significantly higher than the 7.9% in the targeted therapy alone group, suggesting that combined treatment may increase the risk of pulmonary infections. Overall, these findings are consistent with existing literature and further support the important role of combined treatment strategies in improving the prognosis of patients with EGFR-mutant advanced non-small cell lung cancer, while also highlighting the need to pay attention to potential adverse reactions.

5. Conclusion

In conclusion, this study analyzed the efficacy and safety of local radiotherapy in combination with EGFR-TKI therapy for patients with advanced non-small cell lung cancer with effective EGFR-TKI treatment, compared to EGFR-TKI therapy alone. The addition of local radiotherapy significantly prolongs disease progression time, extends survival, and reduces tumor mortality risk. This study also provides theoretical conditions for subsequent clinical trials concerning radiotherapy combined with EGFR-TKIs. However, due to the limited sample size of this study, further research with larger sample sizes or authoritative prospective studies is

needed to validate the choice of timing for radiotherapy intervention and its safety.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Greenhalgh, J., Boland, A., Bates, V., Vecchio, F., Dundar, Y., Chaplin, M., *et al.* (2021) First-Line Treatment of Advanced Epidermal Growth Factor Receptor (EGFR) Mutation Positive Non-Squamous Non-Small Cell Lung Cancer. *Cochrane Database of Systematic Reviews*, **3**, CD010383. https://doi.org/10.1002/14651858.cd010383.pub3

[2] O'Reilly, E.M., Lee, J.W., Zalupski, M., Capanu, M., Park, J., Golan, T., *et al.* (2020) Randomized, Multicenter, Phase II Trial of Gemcitabine and Cisplatin with or without Veliparib in Patients with Pancreas Adenocarcinoma and a Germline *BRCA*/*PALB*2 Mutation. *Journal of Clinical Oncology*, **38**, 1378-1388. https://doi.org/10.1200/jco.19.02931

[3] Miyauchi, E., Morita, S., Nakamura, A., Hosomi, Y., Watanabe, K., Ikeda, S., *et al.* (2022) Updated Analysis of NEJ009: Gefitinib-Alone versus Gefitinib Plus Chemotherapy for Non-Small-Cell Lung Cancer with Mutated *EGFR*. *Journal of Clinical Oncology*, **40**, 3587-3592. https://doi.org/10.1200/jco.21.02911

[4] Hosomi, Y., Morita, S., Sugawara, S., Kato, T., Fukuhara, T., Gemma, A., *et al.* (2020) Gefitinib Alone versus Gefitinib Plus Chemotherapy for Non-Small-Cell Lung Cancer with Mutated Epidermal Growth Factor Receptor: NEJ009 Study. *Journal of Clinical Oncology*, **38**, 115-123. https://doi.org/10.1200/jco.19.01488

[5] Yamamoto, N., Seto, T., Nishio, M., Goto, K., Yamamoto, N., Okamoto, I., *et al.* (2021) Erlotinib Plus Bevacizumab vs Erlotinib Monotherapy as First-Line Treatment for Advanced EGFR Mutation-Positive Non-Squamous Non-Small-Cell Lung Cancer: Survival Follow-Up Results of the Randomized JO25567 Study. *Lung Cancer*, **151**, 20-24. https://doi.org/10.1016/j.lungcan.2020.11.020

[6] Nishio, K., Seto, T., Nishio, M., Reck, M., Garon, E.B., Sakai, K., *et al.* (2021) Ramucirumab Plus Erlotinib versus Placebo Plus Erlotinib in Patients with Untreated Metastatic EGFR-Mutated NSCLC: RELAY Japanese Subset. *JTO Clinical and Research Reports*, **2**, Article ID: 100171. https://doi.org/10.1016/j.jtocrr.2021.100171

[7] Wu, Y.L., Zhou, C., Liam, C.K., Wu, G., Liu, X., Zhong, Z., *et al.* (2015) First-line Erlotinib versus Gemcitabine/cisplatin in Patients with Advanced EGFR Mutation-Positive Non-Small-Cell Lung Cancer: Analyses from the Phase III, Randomized, Open-Label, ENSURE Study. *Annals of Oncology*, **26**, 1883-1889. https://doi.org/10.1093/annonc/mdv270

[8] Zhong, W., Yan, H., Chen, K., Chen, C., Gu, C., Wang, J., *et al.* (2023) Erlotinib versus Gemcitabine Plus Cisplatin as Neoadjuvant Treatment of Stage IIIA-N2 EGFR-Mutant Non-Small-Cell Lung Cancer: Final Overall Survival Analysis of the EMERGING-CTONG 1103 Randomised Phase II Trial. *Signal Transduction and Targeted Therapy*, **8**, Article No. 76. https://doi.org/10.1038/s41392-022-01286-3

[9] Landre, T., Des Guetz, G., Chouahnia, K., Duchemann, B., Assié, J. and Chouaid, C. (2020) First-line Angiogenesis Inhibitor Plus Erlotinib versus Erlotinib Alone for Advanced Non-Small-Cell Lung Cancer Harboring an EGFR Mutation. *Journal of Cancer Research and Clinical Oncology*, **146**, 3333-3339. https://doi.org/10.1007/s00432-020-03311-w

[10] Shi, Y.K., Wang, L., Han, B., Li, W., Yu, P., Liu, Y., *et al.* (2016) First-Line Icotinib

versus Cisplatine/Pemetrexed Plus Pemetrexed Maintenance Therapy in Lung Adenocarcinoma Patients with EGFR Mutation (CONVINCE). *Annals of Oncology*, **27**, vi425. https://doi.org/10.1093/annonc/mdw383.29

[11] Zhou, C., Chen, G., Huang, Y., Zhou, J., Lin, L., Feng, J., *et al.* (2021) Camrelizumab Plus Carboplatin and Pemetrexed versus Chemotherapy Alone in Chemotherapy-Naive Patients with Advanced Non-Squamous Non-Small-Cell Lung Cancer (Camel): A Randomised, Open-Label, Multicentre, Phase 3 Trial. *The Lancet Respiratory Medicine*, **9**, 305-314. https://doi.org/10.1016/s2213-2600(20)30365-9

[12] Blake-Cerda, M., Lozano-Ruíz, F., Maldonado-Magos, F., de la Mata-Moya, D., Díaz-García, D., Lara-Mejía, L., *et al.* (2021) Consolidative Stereotactic Ablative Radiotherapy (SABR) to Intrapulmonary Lesions Is Associated with Prolonged Progression-Free Survival and Overall Survival in Oligometastatic NSCLC Patients: A Prospective Phase 2 Study. *Lung Cancer*, **152**, 119-126. https://doi.org/10.1016/j.lungcan.2020.12.029

[13] Li, S., Zhu, S., Wei, H., Zhu, P., Jiao, Y., Yi, M., *et al.* (2022) The Prospect of Combination Therapies with the Third-Generation EGFR-TKIs to Overcome the Resistance in NSCLC. *Biomedicine & Pharmacotherapy*, **156**, Article ID: 113959. https://doi.org/10.1016/j.biopha.2022.113959

[14] Faehling, M., Achenbach, J., Staib, P., Steffen, U., Tessen, H.W., Gaillard, V.E., *et al.* (2018) Erlotinib in Routine Clinical Practice for First-Line Maintenance Therapy in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC). *Journal of Cancer Research and Clinical Oncology*, **144**, 1375-1383. https://doi.org/10.1007/s00432-018-2649-x

[15] Zheng, L., Wang, Y., Xu, Z., Yang, Q., Zhu, G., Liao, X., *et al.* (2019) Concurrent EGFR-TKI and Thoracic Radiotherapy as First-Line Treatment for Stage IV Non-Small Cell Lung Cancer Harboring EGFR Active Mutations. *The Oncologist*, **24**, 1031-e612. https://doi.org/10.1634/theoncologist.2019-0285

[16] Elamin, Y.Y., Gomez, D.R., Antonoff, M.B., Robichaux, J.P., Tran, H., Shorter, M.K., *et al.* (2019) Local Consolidation Therapy (LCT) after First Line Tyrosine Kinase Inhibitor (TKI) for Patients with EGFR Mutant Metastatic Non-Small-Cell Lung Cancer (NSCLC). *Clinical Lung Cancer*, **20**, 43-47. https://doi.org/10.1016/j.cllc.2018.09.015

[17] Xu, Q., Zhou, F., Liu, H., Jiang, T., Li, X., Xu, Y., *et al.* (2018) Consolidative Local Ablative Therapy Improves the Survival of Patients with Synchronous Oligometastatic NSCLC Harboring EGFR Activating Mutation Treated with First-Line EGFR-TKIs. *Journal of Thoracic Oncology*, **13**, 1383-1392. https://doi.org/10.1016/j.jtho.2018.05.019

[18] Hashimoto, S., Fujii, Y., Ujiie, M., Miyazaki, K., Sato, S., Kodama, T., *et al.* (2023) Refusal of Subsequent Treatment in Patients with EGFR-Mutant Non-Small-Cell Lung Cancer after Response to EGFR-TKIs. *Cancer Diagnosis & Prognosis*, **3**, 251-256. https://doi.org/10.21873/cdp.10209

[19] Kuhl, C.K., Alparslan, Y., Schmoee, J., Sequeira, B., Keulers, A., Brümmendorf, T.H., *et al.* (2019) Validity of RECIST Version 1.1 for Response Assessment in Metastatic Cancer: A Prospective, Multireader Study. *Radiology*, **290**, 349-356. https://doi.org/10.1148/radiol.2018180648

[20] Zhang, P., Duan, J., Bai, H., Wang, Z., Gao, S., Tan, F., *et al.* (2020) Influence of Adjuvant Chemotherapy on Survival for Patients with Stage IB and IIA Non-Small Cell Lung Cancer. *Thoracic Cancer*, **12**, 30-39. https://doi.org/10.1111/1759-7714.13685

[21] (2019) Retracted: The Prognosis Analysis of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Targeted Treatment Combined with Chemotherapy in Smokers with

Nonsmall Cell Lung Cancer. *Journal of Cellular Biochemistry*, **120**, 8798.

[22] SenthilKumar, G., Fisher, M.M., Skiba, J.H., Miller, M.C., Brennan, S.R., Kaushik, S., *et al*. (2020) FGFR Inhibition Enhances Sensitivity to Radiation in Non-Small Cell Lung Cancer. *Molecular Cancer Therapeutics*, **19**, 1255-1265. https://doi.org/10.1158/1535-7163.mct-19-0931

[23] Wrona, A., Dziadziuszko, R. and Jassem, J. (2021) Combining Radiotherapy with Targeted Therapies in Non-Small Cell Lung Cancer: Focus on Anti-EGFR, Anti-Alk and Anti-Angiogenic Agents. *Translational Lung Cancer Research*, **10**, 2032-2047. https://doi.org/10.21037/tlcr-20-552

[24] Wang, Y., Liu, F., Fang, C., Xu, L., Chen, L., Xu, Z., *et al*. (2021) Combination of Rapamycin and SAHA Enhanced Radiosensitization by Inducing Autophagy and Acetylation in NSCLC. *Aging*, **13**, 18223-18237. https://doi.org/10.18632/aging.203226

[25] Brunner, S., Varga, D., Bozó, R., Polanek, R., Tőkés, T., Szabó, E.R., *et al*. (2021) Analysis of Ionizing Radiation Induced DNA Damage by Superresolution dSTORM Microscopy. *Pathology and Oncology Research*, **27**, Article 1609971. https://doi.org/10.3389/pore.2021.1609971

[26] Asan, A., Skoko, J.J., Woodcock, C.C., Wingert, B.M., Woodcock, S.R., Normolle, D., *et al*. (2019) Electrophilic Fatty Acids Impair RAD51 Function and Potentiate the Effects of DNA-Damaging Agents on Growth of Triple-Negative Breast Cells. *Journal of Biological Chemistry*, **294**, 397-404. https://doi.org/10.1074/jbc.ac118.005899

[27] Deville, S.S., Delgadillo Silva, L.F., Vehlow, A. and Cordes, N. (2020) *c*-Abl Tyrosine Kinase Is Regulated Downstream of the Cytoskeletal Protein Synemin in Head and Neck Squamous Cell Carcinoma Radioresistance and DNA Repair. *International Journal of Molecular Sciences*, **21**, Article 7277. https://doi.org/10.3390/ijms21197277

[28] Paidi, S.K., Diaz, P.M., Dadgar, S., Jenkins, S.V., Quick, C.M., Griffin, R.J., *et al*. (2019) Label-Free Raman Spectroscopy Reveals Signatures of Radiation Resistance in the Tumor Microenvironment. *Cancer Research*, **79**, 2054-2064. https://doi.org/10.1158/0008-5472.can-18-2732

[29] Meta, E., Imhof, B.A., Ropraz, P., Fish, R.J., Brullo, C., Bruno, O., *et al*. (2017) The Pyrazolyl-Urea GeGe3 Inhibits Tumor Angiogenesis and Reveals Dystrophia Myotonica Protein Kinase (DMPK) 1 as a Novel Angiogenesis Target. *Oncotarget*, **8**, 108195-108212. https://doi.org/10.18632/oncotarget.22598

[30] Lemine Sow, M., El Yacoubi, H., Moukafih, B., Balde, S., Akimana, G., Najem, S., *et al*. (2020) Frequency and Types of *EGFR* Mutations in Moroccan Patients with Non-Small Cell Lung Cancer. *Tumori Journal*, **107**, 335-340. https://doi.org/10.1177/0300891620964571

[31] Ma, Y., Du, Y., Wang, R., Ji, X., Wu, J., Liu, Y., *et al*. (2020) Analysis of Multigene Detection in Patients with Advanced Lung Adenocarcinoma Using Cytological Specimens. *Pathology—Research and Practice*, **216**, Article ID: 153036. https://doi.org/10.1016/j.prp.2020.153036

[32] Soria, J., Ohe, Y., Vansteenkiste, J., Reungwetwattana, T., Chewaskulyong, B., Lee, K.H., *et al*. (2018) Osimertinib in Untreated *EGFR*-Mutated Advanced Non-Small-Cell Lung Cancer. *New England Journal of Medicine*, **378**, 113-125. https://doi.org/10.1056/nejmoa1713137