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ORIGINAL RESEARCH

Comparison of the Incidence Rate of Radiation Pneumonitis Observed in Patients with Advanced Lung Adenocarcinoma Treated with Simultaneous Thoracic Radiotherapy and 1G/2G/3G EGFR-TKIs

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Purpose: The present study aimed to evaluate the incidence rate of radiation pneumonitis (RP) in patients with advanced lung adenocarcinoma treated with first-generation (1G), second-generation (2G), or third-generation (3G) epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) combined with thoracic radiotherapy (TRT).

Patients and Methods: Patients with advanced lung adenocarcinoma simultaneously treated with 1G/2G/3G EGFR-TKIs and TRT between 2015–2021 at Shandong Cancer Hospital and Institute were screened. The incidence rate of clinical and imaging RP was compared between the three groups.

Results: A total of 200 patients treated with EGFR-TKIs were enrolled in this study, including 100 patients who were treated with 1G EGFR-TKIs, 50 patients who were treated with 2G EGFR-TKIs, and 50 patients who were treated with 3G EGFR-TKIs (patients matched in a 2:1:1 ratio for tumor characteristics). The overall incidence of clinical RP in the 1G, 2G, and 3G EGFR-TKI groups were 29%, 48%, and 28% (p=0.043), respectively, and that of imaging RP were 33%, 58%, and 36% (p=0.010), respectively. The incidence of RP with a clinical grade ≥3 in the three groups were 14%, 28%, and 12% (p=0.055), respectively, and that with an imaging grade ≥3 in the three groups were 11%, 32%, and 10% (p=0.002), respectively. The incidence of clinical RP was higher in the CFRT group than in the SBRT group, with an overall clinical grade of 38% vs 10% (p<0.001) and imaging grade of 46% vs 10% (p<0.001), respectively. In the multivariate analysis, only GTV volume was an independent predictive factor for all risks of clinical and imaging RP. V20 and grouping of 1G/2G/3G EGFR-TKIs were other independent predictive factors for the risk factors of RP for imaging grades.

Conclusion: Compared with 2G EGFR-TKIs combined with TRT, 1G or 3G EGFR-TKIs combined with TRT achieved a lower incidence of RP.

Keywords: EGFR-TKI, molecular targeted therapy, radiation pneumonitis, thoracic radiotherapy, lung adenocarcinoma

Introduction

Classical epidermal growth factor receptor (EGFR) mutations occur in approximately 40–60% of Asian patients with lung adenocarcinoma.[1] EGFR-TKIs have achieved promising therapeutic efficacy and constitute the first-line treatment for advanced EGFR-mutated non-small cell lung cancer (NSCLC) and include first-generation (1G) (erlotinib, gefitinib, and icotinib), second-generation (2G) (afatinib and dacomitinib), and third-generation (3G) (osimertinib and almonertinib) drugs, which have reshaped the treatment of EGFR-mutant lung cancer.[2–4]

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Thoracic radiotherapy (TRT) plays an integral role in the treatment of advanced lung cancer during targeted therapy. Radiation pneumonitis (RP) is one of the commonly side effects of TRT, which may decrease quality of life, lead to pulmonary failure, and become life-threatening. This severely hampers the quality of life and survival of cancer patients. Also, it is a major factor limiting radiation doses in clinical practice, which affects the local control of tumor. The combined use of the two methods resulted in long-term control and reduced the chance of drug resistance in EGFR-mutated NSCLC.[5–7] Despite the survival benefit of combining TKI and radiotherapy, some patients developed RP of grade 2 or worse. However, there are no precise data on the incidence of RP caused by 1G, 2G, or 3G EGFR-TKIs combined with TRT. Moreover, the grading standard for RP was based on the Common Terminology Criteria for Adverse Events (CTCAE) 5.0 grading system for pneumonitis. However, the guideline failed to consider the detailed grading standard in imaging, leading to a bias and disagreement in RP grading, thus resulting in variable rates of RP. To address these issues, we evaluated the incidence rate of RP in patients with NSCLC treated with simultaneous 1G, 2G, or 3G EGFR-TKIs and TRT using clinical and imaging grading methods for RP.

Materials and Methods

Study Design and Patients

We collected the medical records of patients with stage III–IV lung adenocarcinoma who were simultaneously treated with TRT and 1G, 2G, or 3G EGFR-TKIs between 2015-2021. The baseline characteristics, treatment details, and toxicity data of the patients were retrieved from electronic medical records. The inclusion criteria were as follows: (1) EGFR mutation lung adenocarcinoma confirmed through biopsy; (2) stage III–IV according to the 8th edition of the Tumor-Node-Metastasis classification system (patients in stage III were inoperable and unable to tolerate radical radio-chemotherapy); (3) simultaneous treatment with TRT and 1G, 2G, or 3G EGFR-TKIs, wherein simultaneous treatment was defined as continuous use of TRT during EGFR-TKI treatment and is divided into three conditions, namely TRT at the start of EGFR-TKI use (TRT administered within 7 d from the start of EGFR-TKI treatment), in the middle of EGFR-TKI use (TRT administered 7 d after the start of EGFR-TKI treatment), and in the progression after EGFR-TKI use (TRT administered after EGFR-TKI treatment progression); (4) Eastern Cooperative Oncology Group performance status ≤2; and (5) adequate bone marrow and organ function before concurrent TRT and 1G, 2G, or 3G EGFR-TKIs. Meanwhile, the exclusion criteria were as follows: (1) lack of therapy details, (2) previous treatment with immune checkpoint inhibitors, (3) interstitial lung disease, or (4) thoracic reirradiation. This study was performed in accordance with the amended Declaration of Helsinki and was approved and supervised by Shandong Cancer Hospital and Institute. All enrolled patients fulfilled the ethical requirements.

Treatment Protocol

All the enrolled patients underwent conventional fractional radiotherapy (CFRT) or stereotactic body radiation therapy (SBRT) with photon therapy. The technique of IMRT was used with SBRT. Dosimetric data were extracted from the treatment planning system of the Varian equipment (OBI version 4.0). The gross tumor volume (GTV) was contoured to the primary tumor and/or metastatic lymph nodes in the lung and/or metastasis in the thoracic vertebra. The clinical target volume (CTV) included GTV plus a margin of 0.5 cm to encompass the adjacent subclinical or microscopic malignant disease. The planning tumor volume (PTV) was expanded by 0.5 cm from the CTV for patient movement and setup uncertainties. The lung organ-at-risk (OAR) was defined as the whole lung volume, with the exception of GTV. The treatment plan was evaluated using dose-volume histograms. Dosimetric parameters, including V5 and V20, were recorded. As this study aimed to evaluate the incidence rate of RP in patients treated with either of the three generations of EGFR-TKIs combined with TRT, the OARs of heart and spinal cord were not evaluated.

Diagnosis and Classification of RP

We used two methods to comprehensively evaluate RP. The clinical and imaging grades of RP were evaluated according to the CTCAE 5.0 grading system for pneumonitis and pulmonary fibrosis, respectively. The clinical grading of RP was as follows: grade 1, asymptomatic (clinical or diagnostic observations only or intervention not indicated); grade 2,

symptomatic (medical intervention indicated or limiting instrumental activities of daily living [ADL]); grade 3, severe symptoms (limited self-care ADL or oxygen indicated); grade 4, life-threatening respiratory compromise or urgent intervention indicated (eg, tracheotomy or intubation); and grade 5, death. Meanwhile, the imaging grading of RP was as follows: grade 1, radiologic pulmonary pneumonitis <25% of lung volume; grade 2, radiographic pulmonary pneumonitis 25%-50%; grade 3, radiographic pulmonary pneumonitis >50%-75%; grade 4, radiographic pulmonary pneumonitis >75%; and grade 5, death. In addition, we collected the imaging expression of RP as follows: the patchy consolidation and ground-glass opacities were found by CT in the area of lung radiotherapy within 6 months after radiotherapy. Imaging grading and follow-up computed tomography scans were independently evaluated by two senior radiologists, and any differences were resolved by consulting a third senior radiologist. The patients returned to the hospital for efficacy evaluation every month after radiotherapy and then once every 3 months for re-examination or when symptoms such as tightness, suffocation, or cough developed. All lesions were recorded during the screening period. In addition, the tumors and RP were evaluated during screening.

Statistical Analysis

The chi-square test was used to compare the overall incidence of RP, grade ≥3 RP, and clinical data of the patients in the 1G, 2G, and 3G EGFR-TKI groups. Univariate and multivariate logistic regression models were used to analyze risk factors for RP. Hazard ratios and corresponding two-sided 95% confidence intervals were estimated using the Cox proportional hazard model. Meanwhile, for noncategorical variables, receiver operating characteristic curves were generated to determine the optimal cut-off value according to the Youden index. The continuous variables were then converted into categorical variables, and univariate analysis was performed. The patients were censored at the date of the last follow-up visit (February 2022). All statistical analyses were performed using SPSS version 26.0 (IBM Corp, Armonk, NY, USA), Statistical significance was set at p-value <0.05.

Results

Patients and Treatment

A total of 1501 patients with advanced lung adenocarcinoma were screened in this study. All the patients received EGFR-TKI therapy combined with radiotherapy. Of these patients, 889 (59.2%) radiation areas were unirradiated part of the lung, such as brain or bone metastases sites (except for thoracic vertebral metastases), 369 (24.6%) did not receive TRT during EGFR-TKI, 18 (1.2%) were lost to follow-up after receiving TRT, and 25 (1.7%) had baseline characteristics that did not meet the matching standards. Ultimately, 200 patients were included in this study, of which 100 were treated with 1G EGFR-TKIs, 50 were treated with 2G EGFR-TKIs, and 50 were treated with 3G EGFR-TKIs (patients matched in a 2:1:1 ratio for tumor characteristics). Patients in the three groups were simultaneously treated with TRT. The demographics of all patients are presented in Table 1. No differences were observed in the baseline characteristics of age, sex, Karnofsky Performance Scale (KPS) score, smoking index, tumor stage, treatment line of the target drugs, and dose fractionation among the three groups. The median follow-up duration for RP was 15 months in the population.

Of the patients, 37 (18.5%) received TRT at the beginning of EGFR-TKI therapy, 77 (38.5%) received TRT in the middle of EGFR-TKI use, and 86 (43.0%) received TRT in the progression after EGFR-TKI use to improve local control. The median radiotherapy doses in the 1G, 2G, and 3G groups were 56, 54.5, and 54 Gy, respectively. Meanwhile, the median durations of EGFR-TKI treatment before TRT in the 1G, 2G, and 3G groups were 3.9, 3.0, and 5.6 months, respectively. The median times from the beginning of TRT to the occurrence of RP observed via imaging in the three groups was 2.4, 2.5, and 2.8 months, respectively, and that via clinical symptoms was 2.7, 2.9, and 3.4 months, respectively. The mean prescription dose for CFRT and SBRT was 55Gy (IQR 50Gy–60Gy). The number of fractions in SBRT was 10 (IQR 7–10). The mean dose to PTV of CFRT was 145 m^3 (IQR 81.3 m^3–260.7 m^3) and SBRT was 29m^3 (IQR 22 m^3–49.8 m^3). The technique of radiotherapy was IMRT.

Table 1 Demographics and Tumor Features of the Cohort

	1G EGFR-TKI (n=100)	2G EGFR-TKI (n=50)	3G EGFR-TKI (n=50)	*p* value
Age				0.912
<55	43(43%)	28(56%)	30(60%)	
≥55	57(57%)	22(44%)	20(40%)	
Sex				0.642
Female	56(56%)	29(58%)	32(64%)	
Male	44(44%)	21(42%)	18(36%)	
KPS				0.408
>80	69(69%)	33(66%)	29(58%)	
≤80	31(31%)	17(34%)	21(42%)	
Smoking index				0.687
Yes	22(22%)	10(20%)	8(16%)	
No	78(78%)	40(80%)	42(84%)	
Tumor stage				0.633
III	13(13%)	9(18%)	6(12%)	
IV	87(87%)	41(82%)	44(88%)	
Type of mutation				
19del	52(52%)	16(32%)	16(32%)	0.016
L858R	40(40%)	24(48%)	13(26%)	0.071
Treatment line of target drugs				
First line	88(88%)	40(80%)	36(72%)	0.051
Second line	12(12%)	10(20%)	13(26%)	0.090
Third line	0(0%)	0(0%)	1(2%)	0.221
Dose fractionation				0.811
SBRT	14(14%)	9(18%)	8(16%)	
CFRT	86(86%)	41(82%)	42(84%)	

Abbreviations: 1G EGFR-TKI, first-generation epidermal growth factor receptor tyrosine kinase inhibitor; 2G EGFR-TKI, second-generation epidermal growth factor receptor tyrosine kinase inhibitor; 3G EGFR-TKI, third-generation epidermal growth factor receptor tyrosine kinase inhibitor; CFRT, conventionally fractionated radiation therapy; KPS, Karnofsky performance score; SBRT, stereotactic body radiation therapy.

Incidence of RP

The overall incidence of clinical RP in the 1G, 2G, and 3G EGFR-TKI groups was 29 (29%) vs 24 (48%) vs 14 (28%) (p=0.043), respectively, and that of imaging RP was 33 (33%) vs 29 (58%) vs 18 (36%) (p=0.010), respectively. The incidence of RP with a clinical grade ≥3 in the three groups was 14 (14%) vs 14 (28%) vs 6 (12%) (p=0.055), and that of RP with an imaging grade ≥3 in the three groups was 11 (11%) vs 16 (32%) vs 5 (10%) (p=0.002), respectively (Table 2 and Figure 1). Among the 58 patients with both clinical and imaging assessments of RP, the median time from TRT to imaging assessment of RP was 62 days, and the median time of RP according to the clinical symptoms was 84 days (p=0.0397; Figure 2). The incidence of clinical RP was higher in the CFRT group than in the SBRT group, with an overall clinical grade

Table 2 The Incidence of RP

	1G EGFR-TKI (n=100)	2G EGFR-TKI (n=50)	3G EGFR-TKI (n=50)	*p* value
Overall incidence of RP				
Clinical RP	29(29%)	24(48%)	14(28%)	**0.043**
Imaging RP	33(33%)	29(58%)	18(36%)	**0.010**
The incidence of RP with grade ≥3				
Clinical RP	14(14%)	14(28%)	6(12%)	0.055
Imaging RP	11(11%)	16(32%)	5(10%)	**0.002**

Note: The bold text was significantly correlated with RP and the *p* value<0.05.
Abbreviations: 1G EGFR-TKI, first-generation epidermal growth factor receptor tyrosine kinase inhibitor; 2G EGFR-TKI, second-generation epidermal growth factor receptor tyrosine kinase inhibitor; 3G EGFR-TKI, third-generation epidermal growth factor receptor tyrosine kinase inhibitor; RP, radiation pneumonitis.

of 38% vs 10% ($p<0.001$) and imaging grade of 46% vs 10% ($p<0.001$), respectively. The probability of RP with an overlap time ≥30 days was higher than that within 30 days (clinical RP: 45% vs 22%, $p=0.001$; imaging RP: 57% vs 24%, $p<0.001$). In addition, no significant differences were observed in the following ($p>0.05$) (Supplementary Table 1): type of mutation, namely 19del and L858R (clinical RP: 32% vs 40%, $p=0.284$; imaging RP: 42% vs 45%, $p=0.628$); the timing of TRT after

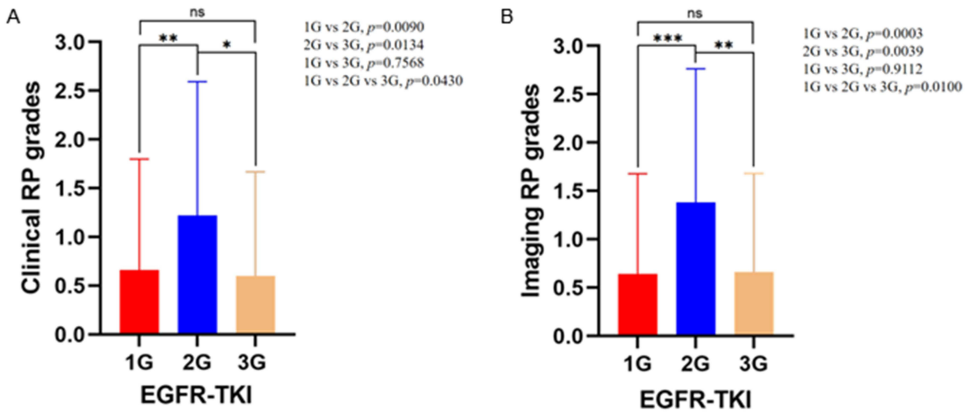

Figure 1 Clinical and imaging grades of RP observed in patients treated with simultaneous TRT and 1G, 2G, or 3G EGFR-TKI. (**A**) Clinical grades of RP caused by simultaneous EGFR-TKI and TRT. (**B**) Imaging grades of RP caused by simultaneous EGFR-TKI and TRT.
Notes: ns $p>0.05$; *$p<0.05$; **$p<0.01$; ***$p<0.001$.
Abbreviations: 1G, first-generation;2G, second-generation; 3G, third-generation; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; ns, no significance; RP, radiation pneumonitis; TRT, thoracic radiotherapy.

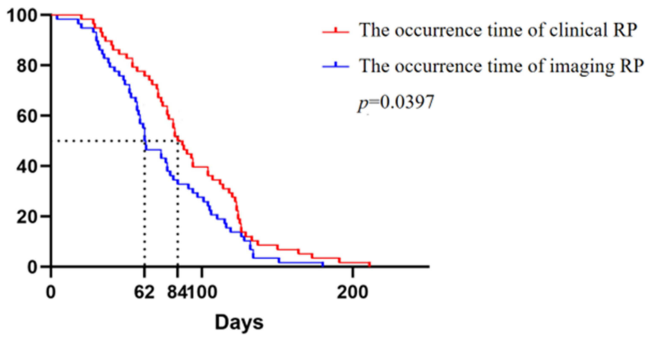

Figure 2 The time of occurrence of both clinical symptoms and imaging features indicating RP. Among the 58 patients with both clinical and imaging assessments of RP, the median time from TRT to imaging assessment of RP was 62 days, and the median time of RP according to the clinical symptom was 84 days ($p=0.0397$).
Abbreviations: RP, radiation pneumonitis; TRT, thoracic radiotherapy.

EGFR-TKI use, that is, the beginning of EGFR-TKI use, in the middle of EGFR-TKI use, and in the progression after EGFR-TKI use (clinical RP: 27% vs 39% vs 31%, p=0.387; imaging RP: 43% vs 43% vs 36%, p=0.611); tumor stage, including stage III and IV (clinical RP: 36% vs 33%, p=0.789; imaging RP: 50% vs 38%, p=0.244); and area of the TRT, including the upper, middle, and lower lobe (clinical RP: 37% vs 34% vs 26%, p=0.420; imaging RP: 37% vs 34% vs 26%, p=0.571).

Risk Factors of RP

In univariate analysis, age, sex, KPS, and smoking index were not associated with RP. Meanwhile, overlap time ≥30 days, dose fractionation, radiation therapy dose, GTV, V5, and V20 were significantly correlated with the incidence of RP and grade ≥3 of RP (Table 3 and Table 4). In the multivariate analysis, only GTV volume was an independent predictive factor for all risks of clinical and imaging RP. V20 and grouping of 1G/2G/3G EGFR-TKIs were other independent predictive factors for the risk factors of RP for imaging grades.

Table 3 Univariate and Multivariate Logistic Regression Analysis of the Risk Factors of RP

Factor	Clinical Grades				Imaging Grades			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	p value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)
Age								
<55								
≥55	0.051	1.841(0.997–3.398)			**0.020**	2.009(1.115–3.620)		
Sex								
Male								
Female	0.953	0.982(0.541–1.782)			0.349	1.318(0.739–2.351)		
KPS								
>80								
≤80	0.364	1.327(0.720–2.445)			0.627	0.862(0.474–1.569)		
Smoking index								
No								
Yes	0.549	1.246(0.606–2.562)			0.718	1.138(0.564–2.298)		
COPD	0.083	2.425(0.890–6.604)			0.260	1.775(0.654–4.813)		
Thoracic surgery	0.399	0.634(0.220–1.827)			>0.999	0.999(0.389–2.568)		
Overlap time								
<30d								
≥30d	**0.001**	2.888(1.565–5.326)			**<0.001**	4.086(2.234–7.471)		
The timing of adding TRT after EGFR-TKIs use								
In the beginning of EGFR-TKIs use	0.357	0.689(0.311–1.523)			0.656	1.179(0.572–2.427)		
In the middle of EGFR-TKIs use	0.196	1.484(0.815–2.699)			0.514	1.213(0.679–2.165)		
In the progression after EGFR-TKIs use	0.584	0.847(0.466–1.537)			0.322	0.748(0.420–1.329)		
Type of mutation								
19del	0.729	0.900(0.495–1.635)			0.682	1.127(0.636–1.998)		
L858R	0.110	1.629(0.895–2.963)			0.214	1.444(0.809–2.579)		

(*Continued*)

Table 3 (Continued).

Factor	Clinical Grades				Imaging Grades			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	p value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)
Area (lobe)								
Upper lobe	0.295	1.371(0.759–2.475)			0.603	1.162(0.659–2.048)		
Middle lobe	0.925	1.034(0.510–2.097)			0.626	1.184(0.601–2.331)		
Lower lobe	0.204	0.637(0.317–1.279)			0.296	0.705(0.366–1.359)		
Dose fractionation								
SBRT								
CFRT	**0.006**	5.689(1.662–19.474)			**0.001**	7.812(2.287–26.686)		
Radiationtherapy dose								
<53.15								
≥53.15	**0.049**	1.874(1.003–3.501)			**0.012**	2.168(1.187–3.961)		
GTV								
<28.35								
≥28.35	**<0.001**	3.012(1.620–5.601)	**0.014**	2.330(1.186–4.576)	**<0.001**	5.571(2.968–10.460)	**<0.001**	4.448(2.246–8.807)
V5								
<33.5								
≥33.5	**0.003**	2.543(1.387–4.661)			**<0.001**	3.196(1.759–5.808)		
V20								
<17.5								
≥17.5	**0.001**	3.033(1.558–5.903)			**<0.001**	4.039(2.045–7.978)	**0.023**	3.043(1.170–7.914)
Grouping of 1G/2G/3G EGFR-TKIs	0.752	1.059(0.744–1.507)			0.385	1.163(0.828–1.634)	**0.035**	1.564(1.032–2.369)

Note: The bold text was some risk factor of RP, which were significantly correlated with RP and the *p* value<0.05.
Abbreviations: CFRT, conventionally fractionated radiation therapy; COPD, Chronic obstructive pulmonary disease; d, days; GTV, Gross tumor volume; KPS, Karnofsky performance score; SBRT, stereotactic body radiation therapy; TRT, thoracic radiotherapy.

Discussion

Recent data indicate that EGFR-TKIs combined with TRT are effective for patients with advanced non-squamous cell lung cancer; however, the combined use of these two treatment strategies increase the incidence rate of RP.

The 1G EGFR TKIs demonstrated an objective response rate of 56%–83%, with a median progression-free survival (PFS) of 9.7–13.1 months.[2,8–10] However, most patients inevitably developed progressive disease within 1 year of treatment due to acquiring resistance. The most dominant mechanism is the development of acquired EGFR T790M mutation.[11] Afatinib is an oral irreversible ErbB family blocker that has demonstrated efficacy and tolerable toxicity in EGFR mutation-positive advanced lung adenocarcinoma, with a median PFS of 11.0–13.4 months.[3,12] This is a significantly improved outcome in treatment-naive patients with EGFR-mutated NSCLC compared with 1G EGFR-TKIs.[13] Notably, afatinib demonstrated activity against major uncommon mutations, with a median time to treatment failure of 10.8–14.7 months for compound mutations.[14] Nevertheless, EGFR T790M is also the dominant resistance mechanism in afatinib. As a first-line treatment for EGFR mutations, the 3G EGFR-TKI osimertinib specifically and irreversibly binds to the EGFR kinase domain, especially EGFR T790M resistance mutations, while sparing wild-type EGFR and the toxicities associated with its inhibition, with a median PFS (mPFS) of 18.9–20.5 months. Thus,

Table 4 Univariate and Multivariate Logistic Regression Analysis of the Risk Factors of ≥3 RP

Factor	Clinical Grades				Imaging Grades			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	p value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)
Age								
<55								
≥55	0.352	1.439(0.668–3.099)			0.164	1.774(0.792–3.976)		
Sex								
Male								
Female	0.471	0.761(0.363–1.598)			0.778	0.896(0.418–1.922)		
KPS								
>80								
≤80	0.915	1.043(0.482–2.259)			0.987	0.993(0.448–2.202)		
Smoking index								
No								
Yes	0.303	1.568(0.666–3.690)			0.847	0.910(0.347–2.385)		
COPD	**0.044**	3.019(1.033–8.830)			**0.006**	4.424(1.542–12.693)		
Thoracic surgery	0.388	0.514(0.114–2.326)			0.446	0.556(0.122–2.521)		
Overlap time								
<30d								
≥30d	**0.017**	2.600(1.190–5.676)			**0.038**	2.311(1.049–5.093)		
The timing of adding TRT after EGFR-TKIs use								
In the beginning of EGFR-TKIs use	0.731	1.175(0.468–2.951)			0.968	1.020(0.387–2.689)		
In the middle of EGFR-TKIs use	0.725	1.144(0.540–2.426)			0.899	0.951(0.436–2.074)		
In the progression after EGFR-TKIs use	0.538	0.789(0.370–1.681)			0.926	1.037(0.484–2.223)		
Type of mutation								
19del	0.626	0.828(0.389–1.766)			0.342	0.682(0.309–1.503)		
L858R	0.133	1.767(0.840–3.714)			**0.027**	2.375(1.103–5.144)		
Area (lobe)								
Upper lobe	0.854	1.072(0.512–2.245)			0.853	931(0.437–1.983)		
Middle lobe	0.827	0.904(0.365–2.241)			0.985	0.991(0.397–2.473)		
Lower lobe	0.997	0.998(0.433–2.303)			0.820	1.103(0.474–2.564)		
Dose fractionation								
SBRT								
CFRT	0.107	3.387(0.768–14.933)			0.132	3.129(0.708–13.834)		
Radiationtherapy dose								
<53.15								
≥53.15	0.092	2.025(0.890–4.607)			0.300	1.533(0.683–3.441)		

(*Continued*)

Table 4 (Continued).

Factor	Clinical Grades				Imaging Grades			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	p value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)
GTV								
<28.35								
≥28.35	**0.014**	2.708(1.219–6.015)	**0.047**	0.416(0.175–0.987)	**0.002**	4.221(1.731–10.292)	**0.007**	3.686(1.420–9.564)
V5								
<33.5								
≥33.5	0.102	1.862(0.885–3.919)			0.050	2.149(1.002–4.613)		
V20								
<17.5								
≥17.5	0.245	1.611(0.721–3.602)			0.066	2.124(0.951–4.744)		
Grouping of 1G/2G/3G EGFR-TKIs	0.910	1.026(0.658–1.599)			0.642	1.113(0.709–1.746)		

Note: The bold text was some risk factor of RP, which were significantly correlated with RP and the *p* value<0.05.
Abbreviations: CFRT, conventionally fractionated radiation therapy; COPD, Chronic obstructive pulmonary disease; d, days; GTV, Gross tumor volume; KPS, Karnofsky performance score; SBRT, stereotactic body radiation therapy; TRT, thoracic radiotherapy.

osimertinib is a standard therapy for patients with previously untreated EGFR mutation-positive advanced NSCLC.[15,16] Currently, three generations of EGFR-TKIs are recommended for the treatment of EGFR mutation-positive patients according to the National Comprehensive Cancer Network guidelines (version 3.2022).[17]

A previous study on gefitinib and erlotinib with simultaneous TRT showed that the incidence of RP was approximately 84% (21/25) and the incidence rate of grade ≥3 RP reached 12%.[18] Recently, a phase 2 trial on the combination of erlotinib and TRT in locally advanced or metastatic NSCLC showed feasibility and favorable safety profile, with an incidence of grade ≥3 RP of approximately 16%.[19] A study of osimertinib combined with TRT reported RP in all 11 patients, and the grade ≥3 RP rate reached 55%.[20] This phenomenon might be related to the small sample size, which led to bias that might influence the results, and the lacked of a unified imaging evaluation of RP. In contrast with the high incidence of RP in the above studies, a retrospective study showed a low incidence of RP (7.7% of cases) in patients treated with combination of gefitinib, icontinib, erlotinib, and TRT.[21] Another prospective study suggested that 1G EGFR-TKI simultaneous with TRT caused a 39% incidence of RP (10/26) and a 4% incidence of grade ≥3 RP.[7] In a Phase II study, 32.1% (9/28) of the patients experienced grade 1 or 2 pneumonitis, and there was no grade 3 acute irradiation pneumonitis in patients treated with radiotherapy combined with gefitinib.[6] Furthermore, a clinical trial also showed a low frequency of symptomatic RP, with an incidence of 10.3% (7/68), and the grade ≥3 RP rate reached 5.9% (4/68).[22] Based on literature, we found that the data on RP have been inconclusive and that a small sample size has been used in current studies of the simultaneous use of EGFR-TKIs and TRT, limiting further analysis and causing a lack of data comparing the combination of TRT with three generations of EGFR-TKIs. To the best of our knowledge, this study is the first to compare the incidence of RP among the three types of EGFR-TKIs combined with TRT and represents the largest study to date. Our study showed that 2G EGFR-TKIs combined with TRT resulted in a higher rate of RP than 1G or 3G EGFR-TKIs combined with TRT, indicating that the latter two are safe options for patients with EGFR mutations.

The pathogenesis of RP induced by EGFR-TKIs combined with TRT remains unclear. EGFR-TKIs may enhance lung injury by blocking EGFR transactivation, thereby enhancing lung epithelial cell apoptosis and lymphocytic inflammation and preventing their self-repair in response to radiation damage, leading to inflammatory cell recruitment and consequent tissue injury.[23] Thus, the addition of TRT may suppress the proliferation of alveolar epithelial cell self-repair. In the present study, we found that afatinib, which can covalently modify EGFR, had the highest incidence of RP. Afatinib is an orally bioavailable ErbB family blocker that irreversibly blocks signaling from EGFR/ErbB1, human epidermal growth

factor receptor 2 (HER2/ErbB2), and ErbB4, and has wide-spectrum preclinical activity against EGFR mutations.[24,25] Owing to their covalent bond binding mechanism, 2G EGFR-TKIs have a higher binding power and are difficult to dissociate from EGFR, which may be one of the mechanisms underlying the high occurrence of adverse reactions to afatinib.[26] Future research could be based upon a larger survey sample at the individual level by a prospective study, providing a theoretical reference for further study on the mechanism of RP.

Several observations are worth highlighting. First, our study showed that 58 (29%) patients with both clinical symptoms and imaging diagnosis showed RP after radiotherapy, and we used the Kaplan-Meier test to compare the difference in the time of RP after radiotherapy in the three groups. We found that the imaging occurrence of RP presented earlier than the clinical symptoms (p=0.0397), indicating that serial radiological assessment, such as high-resolution computed tomography during EGFR-TKI treatment, is an effective method for the early detection of RP-related changes as well as the prediction of clinical symptoms of RP, which can alleviate or prevent patient discomfort. Second, a recent study showed that overlap time was an independent risk factor for RP in patients treated with simultaneous EGFR-TKI and TRT, suggesting that shortening the overlap time might reduce the rate of RP.[27] In the current study, we found that an overlap time of EGFR-TKI and TRT within 30 days significantly decreased the incidence of clinical and imaging RP, which may be because of the reduced interaction between drugs, radiation, and lung tissue due to shorter exposure time. Third, SBRT plays a major role in the treatment of oligometastatic disease in the lungs due to its high local control and low toxicity, and most patients who undergo SBRT have smaller lesions than those who undergo CFRT.[26,27] Univariate logistic regression analysis showed that the incidence of RP was higher in patients undergoing CFRT than in those receiving SBRT, and this phenomenon may be attributed to the lower dose to the OARs and significantly reduced treatment time with SBRT.

Univariate and multivariate logistic regressions showed that the GTV was an independent predictive factor, indicating that a smaller GTV may lower the incidence of RP. Based on our results, the use of SBRT and TRT within 30 days, smaller GTV, and V20 can significantly reduce the chances of RP; thus, we speculate that when patients got the smallest tumor volume under the EGFR-TKIs treatment, at this moment TRT which may be the best timing to reduce the incidence of RP.

Despite these findings, the present study had some limitations. Firstly, 200 of the patients included in the analysis were published cases studies and this may introduce bias as it is more likely that positive cases are published. Secondly, EGFR mutation detection platforms vary widely and different testing methods have been used across studies in our analysis. This may have introduced some unrecognized biases.

Conclusion

In conclusion, compared with 2G EGFR-TKIs, 1G or 3G EGFR-TKIs combined with TRT achieved a lower incidence of RP. In addition, a smaller radiation exposure area can reduce the incidence of RP. The imaging manifestation of RP occurs earlier than the clinical symptoms, suggesting that imaging findings can provide an early warning of clinical symptoms.

Abbreviations

1G, first-generation; 2G, second-generation; 3G, third-generation; CFRT, conventional fractional radiotherapy; CTCAE, Common Terminology Criteria for Adverse Events; CTV, clinical target volume; EGFR, epidermal growth factor receptor; EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; GTV, gross tumor volume; KPS, Karnofsky Performance Scale; mPFS, median PFS; NSCLC, non-small cell lung cancer; OAR, organ-at-risk; PFS, progression-free survival; PTV, planning tumor volume; RP, radiation pneumonitis; SBRT, stereotactic body radiation therapy; TRT, thoracic radiotherapy.

Ethics Approval and Consent to Participate

The present study was approved by the Ethics Committee of Shandong Cancer Hospital and Institute (approval number: SDTHEC2021003186). Informed consent was waived due to the retrospective design. The present study was performed in accordance with the principle of the 1975 Declaration of Helsinki and its later amendments or comparable ethical standards, and data confidentiality was ensured. The date was anonymized for this study. Due to the retrospective nature of the study, informed consent was waived by the Ethics Committee of Shandong Cancer Hospital and Institute.

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Disclosure

The authors report no conflicts of interest in this work.

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