Radiation Oncology

RESEARCH

Open Access

Risk factors for radiation pneumonitis in NSCLC patients treated with third-generation EGFR TKIs and chest radiotherapy

Nan Zhao[1†], Liang Xiong[2,3†], Xuehong Bai[3], Wenyan Pan[3], Ping Hai[3], Hongqiang Ye[3], Ting Zhao[3], Kai Cui[1], Rong Ma[3] and Yanyang Wang[3,4*]

Abstract

Background Non-small cell lung cancer (NSCLC) patients receiving third-generation EGFR TKIs with thoracic radiotherapy (TRT) significantly prolong survival and also increase the incidence of radiation pneumonitis (RP). The aim of our study was to investigate the incidence and risk factors of RP in NSCLC patients receiving third-generation EGFR TKIs and TRT.

Patients and methods We retrospectively evaluated NSCLC patients who received both third-generation EGFR TKIs and TRT at the General Hospital of Ningxia Medical University from January 2023 to September 2024. RP was diagnosed by clinical symptoms on computed tomography (CT) scans and graded according to the Common Terminology Criteria for Adverse Events 5.0. Risk factors for RP were determined by univariate and multivariate logistic regression analysis.

Results Of the 42 patients included, 26 (61.9%) developed RP and 14 (33.3%) developed grade ≥ 2 RP. Grade ≥ 2 RP all occurred within 6 months of receiving TRT, and the median time from TRT to RP was 3.69 months (2–10 months). GTV ≥ 39 ml and total lung V20 ≥ 14.95% were found to be independent risk factors for RP development.

Conclusion The strategy of combining a third-generation TKI with TRT significantly increases the incidence of RP, and the risk of RP in these patients can be reduced by adjusting lung radiation dosimetry parameters. In NSCLC patients taking triple-generation TKIs with primary tumour progression, the timing and dose of TRT addition must be strictly controlled to optimise the therapeutic strategy and reduce the incidence of RP.

Clinical trial number Not applicable.

Keywords Radiation pneumonitis, Third-generation EGFR TKIs, Chest radiotherapy, Non-small cell lung cancer, Risk factors

†Nan Zhao and Liang Xiong contributed equally to this work.

*Correspondence:
Yanyang Wang
fdwyy1981@163.com
[1]Master Training Station, General Hospital of Ningxia Medical University, Yinchuan, China
[2]Graduate School of Ningxia Medical University, Yinchuan, China
[3]Department of Radiation Oncology, General Hospital of Ningxia Medical University, Yinchuan, China
[4]Cancer Institute, General Hospital of Ningxia Medical University, Yinchuan, China

Background

Non-small cell lung cancer (NSCLC) accounts for approximately 80–85% of lung cancers and is one of the major causes of cancer mortality in China [1]. With the increasing understanding of NSCLC, NSCLC treatment has entered the era of molecular therapy based on driver genes such as EGFR mutation, KRAS mutation, ROS1 fusion, ALK fusion [2–3]. EGFR mutations, with exon 19 deletions and exon 21 L858R point mutations accounting for 90%, are the most common driver gene mutations in Asian lung cancer patients [4].

Despite the significant prolongation of patient survival following treatment with first- and second-generation EGFR TKIs, resistance is inevitable at approximately 8–14 months [5], with T790M mutations accounting for 50% of the resistance mechanisms [6]. In response to T790 mutation resistance, in November 2018, the 2019 edition of the National Comprehensive Cancer Network (NCCN) NSCLC guidelines identified third-generation EGFR TKIs, represented by osimertinib, as the first-line treatment option for EGFR-positive patients [7]. With the continued development of third-generation EGFR TKIs, the median progression-free survival (mPFS) of NSCLC patients has been extended to 9.6–12.4 months with a median Overall survival (OS) of 22.1–30.2 months [8–9]. However, tertiary EGFR mutations (C797S, L792, exon 20 insertion), activation of bypass pathways (MET and HER2/HER3 upregulation) and histological transformation-driven, the above mechanisms of acquired resistance are still a challenge [10–17]. And further strategies combining chemotherapy, radiotherapy, MET inhibitors and immunotherapy are needed to address patient resistance in practice. Considering that 41.25% of patients with EGFR-mutant NSCLC relapse at the primary site and have a high propensity to metastasise [18], and that triple-generation EGFR TKIs can improve radiosensitivity [19]. Previous studies have also shown that the addition of SBRT significantly postponed the occurrence of acquired resistance to EGFR TKIs and prolonged the PFS and OS of patients. Radiotherapy of the primary lesion alone might be more beneficial than that of metastatic sites [20].

Therefore, we often combine TRT with third-generation EGFR TKIs, but there are still many questions about the optimal timing, technique, dose and side effects of radiotherapy. Early clinical data showed that the combination of both may increase the incidence of RP [21–22]. In addition, a recent retrospective analysis by Zhu Hui et al. [23] showed that NSCLC patients receiving both aumolertinib and TRT had a 42.9% incidence of radiation pneumonitis, with GTV ≥ 21 ml and ipsilateral lung V20 ≥ 25% as independent risk factors for the development of RP. The incidence of clinical RP has not been effectively and fully evaluated as the combination of triple-generation TKIs with TRT has introduced new treatment strategies for NSCLC patients. Therefore, our study aimed to evaluate the incidence of RP in NSCLC patients treated with combined third-generation EGFR TKIs and TRT, and to investigate and analyse associated risk factors.

Patients and methods

Study design and patients

We retrospectively analysed NSCLC patients admitted to the General Hospital of Ningxia Medical University from January 2023 to September 2024. Inclusion criteria included (1) NSCLC patients with stage IIIb-IV NSCLC with EGFR gene mutation; (2) concurrently receiving triple-generation EGFR TKIs and TRT; (3) ECOG functional status score of 0 or 1. Exclusion criteria included (1) prior history of chest radiotherapy; (2) prior combination of lung diseases; (3) prior treatment with immune checkpoint inhibitors; (4) concomitant administration of drugs that clearly have the ability to cause pulmonary fibrosis. Fifty-three patients with NSCLC were initially enrolled in this study, of whom eight were lost to follow-up and three were unable to obtain lung radiation dosimetry parameters. Forty-two patients were finally included, including 3 patients with stage IIIb disease and 39 patients with stage IV disease. There were 21 men and 21 women. Four patients underwent surgery, including one patient who underwent surgery after neoadjuvant chemotherapy. Concurrent therapy was defined as an EGFR triplet TKI overlapping with TRT for at least one day. The study was approved by the Ethical Review Committee of the General Hospital of Ningxia Medical University and was conducted in accordance with the Declaration of Helsinki.

Treatment protocol

All patients with NSCLC were treated with a third-generation EGFR TKIs as first or second-line treatment, including osimertinib 80 mg/d, aumolertinib 110 mg/d and furmonertinib 80 mg/d until intolerable serious adverse events occurred. The primary endpoint of this study was the occurrence of RP, Gross tumor volume (GTV) defined as the primary tumour visible on CT and planned target volume (PTV) defined as a homogeneous outgrowth of 0.8 cm above the GTV. Lung dose was defined as the volume of lung tissue that received radiation at a dose greater than or equal to this dose as a percentage of the total lung tissue volume. The above lung radiation dosimetric parameters were extracted from the Dose-volume histogram (DVH) of the treatment planning system.

Diagnosis of RP

The diagnosis of RP is based on history, clinical symptoms and imaging changes, and excludes factors such as primary tumour progression, lung infection, acute exacerbation of chronic obstructive pulmonary disease, and drug-induced pneumonia. The diagnosis was made jointly by two senior physicians, and in cases of disagreement between the two physicians, the judgement was re-examined after discussion with a third physician. The severity of RP was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) 5.0 [24], as shown in Table 1.

Statistical analyses

Binary logistic regression analysis was used to explore the association between RP and factors, and categorical variables were entered directly into one-way regression analysis. For continuous variables, receiver operating characteristic (ROC) curves were plotted, and after considering specificity and sensitivity, the maximum Jordan index was used as the optimal cut-off value, which was transformed into categorical variables for one-way analysis. Finally, variables with significant effects in the univariate analysis were included in the multivariate logistic regression analysis. $P < 0.05$ was considered a statistically significant difference. All data were analysed using SPSS 27.0 medical statistical software.

Results

Patient characteristics

A total of 42 patients were enrolled from January 2023 to September 2024, with the last follow-up in January 2025. There were 50% men and 50% women. There were 36 patients (85.7%) who were smokers, and the primary tumour was located in the lower lobe in 33.3% of patients. The median age was 58.5 years (range, 36–82 years) and the median interval between TKIs and TRT was 10.5 months (range, 0–96 months). Baseline patient characteristics are shown in Table 2.

Radiation details

Of the 42 patients, 19 patients (45.2%) received volumetric modulated arc therapy (VMAT). The same 19 patients (45.2%) received intensity-modulated radiotherapy (IMRT), while 3 patients (7.2%) and 1 patient (2.4%) received tomotherapy (TOMO) and three-dimensional conformal radiotherapy (3D-CRT), respectively. The median total dose was 50 Gy (range, 32–60 Gy), delivered in a median of 25 fractions (range, 6–30) with a median dose per fraction of 2 Gy (range, 2–8 Gy). The median GTV and PTV were 25.5 ml (range, 3.15-213.13 ml) and 149.83 ml (range, 1.74-460.52 ml), respectively. The median mean lung dose (MLD) was 8.46 Gy (range, 1.03–13.67 Gy). As shown in Table 2.

Association between clinical characteristics and RP

Of the 42 NSCLC patients included, 26 patients (61.9%) developed RP, including 12 patients with grade 1 RP and

Table 1 Grading criteria for radiation pneumonitis

Grade	Clinical Features	Imageological change
1	There were no symptoms, only imaging changes, and no treatment.	Ground-glass opacities with < 25% pulmonary parenchymal involvement were observed.
2	Symptoms occurred and daily activities were slightly limited, and symptomatic treatment was given.	Extensive ground-glass opacities, with or without small focal consolidation, and 25%-50% of the lung parenchyma were involved.
3	The symptoms were severe, daily activities were limited, and oxygen therapy was needed.	There was marked focal consolidation with or without fibrosis, and 50% to 75% of the lung parenchyma was involved.
4	Life-threatening respiratory impairment requires urgent intervention and mechanical ventilation if necessary.	Severe pulmonary complications occurred, with > 75% pulmonary parenchymal involvement with severe cellular changes.
5	Die.	Died of radiation-induced pulmonary fibrosis.

Table 2 Clinical baseline characteristics of 42 patients

Characteristic	n (%) (N=42)
Gender	
Male	21(50%)
Female	21(50%)
Median age (years) (range)	58.5(36-82)
Median BMI (range)	23.02(16.42-29.39)
Smoking history	
Yes	6(14.3%)
No	36(85.7%)
Disease stage	
IIIb	3(7.1%)
IV	39(92.9%)
Location of the primary site	
Not included lower lob	28(66.7%)
Lower lob	14(33.3%)
Surgery history	
Yes	4(9.5%)
No	38(90.5%)
Chemotherapy history	
Yes	35(83.3%)
No	7(16.7%)
Median targeted radiotherapy interval (m) (range)	10.5(0-96)
Median total dose (Gy) (range)	50(32-60)
Median dose per fraction (Gy) (range)	2(2-8)
Median number of fraction (range)	25(6-30)
Median GTV size (ml) (range)	25.5(3.15-213.13)
Median PTV size (ml) (range)	149.83(1.74-460.52)
Median total MLD (Gy) (range)	8.46(1.03-13.67)
Time of TRT before RP(m)(range)	3.69(2-10)

GTV gross tumor volume; PTV planning target volume; MLD median lung dose; TRT thoracic radiotherapy; RP Radiation pneumonitis.

11 and 3 patients with grade 2 and 3 RP, respectively. Fig. 1 shows a typical CT image of a patient who developed grade 3 RP, with RP occurring 2 months after radiotherapy. The total dose of chest radiotherapy received by this patient was 50 Gy at 2 Gy in 25 fractions. The total mean lung dose (MLD) of 7.54 Gy on TRT, an ipsilateral lung V20 of 31.33%, and a total lung V20 of 12.42%. Univariate analysis of all clinical factors was performed and as shown in the results in Table 3. There was no statistically significant difference between whether patients developed RP and factors including sex, age, BMI, smoking history, primary tumor stage and location, type of third-generation EGFR TKIs, previous combined surgery and chemotherapy ($P > 0.05$).

Risk factors for ≥ grade 2 RP

The 14 NSCLC patients who developed grade ≥ 2 RP were all stage IV. Ten of them were female, and 2 patients had a history of smoking. We found that the median time from initiation of TRT to development of RP was 3.69 months (range, 2–10 months), and all patients with grade ≥ 2 RP developed RP within 6 months of receiving TRT. Continuous variables were transformed into categorical variables by assessing the predictive ability of continuous

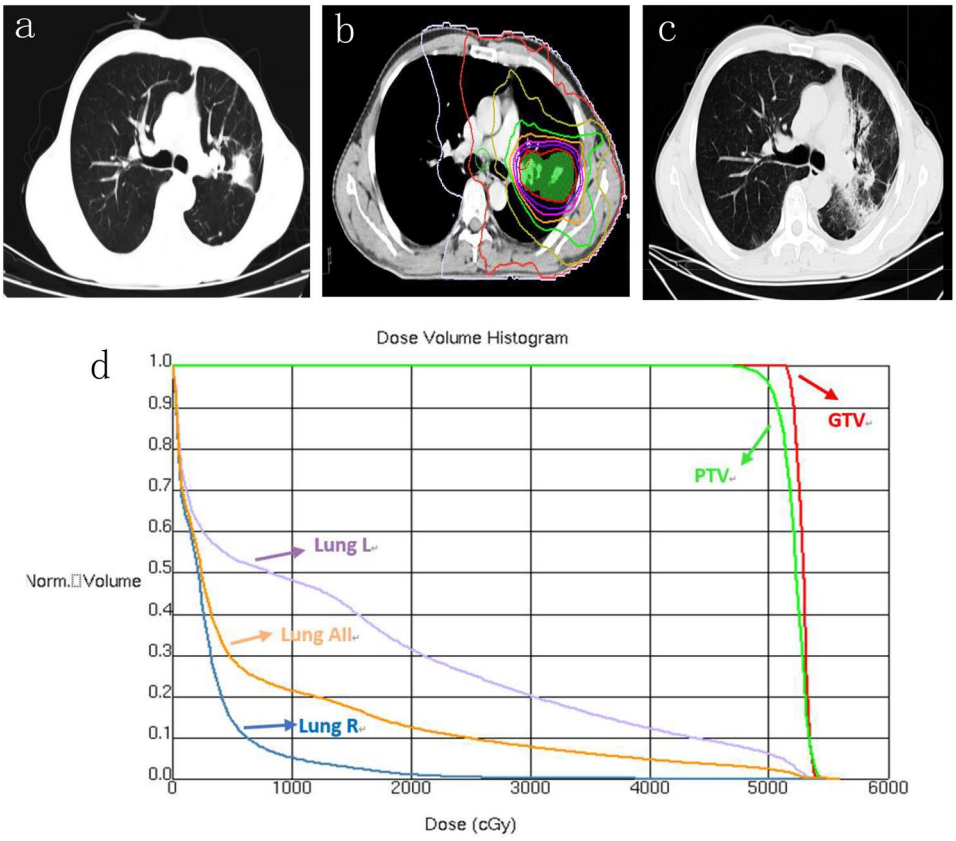

Fig. 1 Representative images of one patient who experienced grade 3 RP after TRT. (**a**). Primary lesion. (**b**). Treatment plan. (**c**). Two months after radiotherapy. (**d**). Dose distribution histogram of the GTV, PTV, total lung, right lung and left lung

variables based on the area under the ROC curve (AUC) and calculating the optimal cut-off value based on the maximum Jordan index, as shown in Fig. 2.

The results of one-way logistic regression analyses of ≥2 levels of RP are shown in Table 4 for GTV (OR 0.18; 95% CI 0.03–0.98, $P=0.047$), ipsilateral lung V15 (OR 4.89; 95% CI 1.11–21.47, $P=0.036$), V20 (OR 8.00; 95% CI 1. 50-42.65, $P=0.015$), V30 (OR 4.89; 95% CI 1.22–19.65, $P=0.025$), and total lung V20 (OR 4.50; 95% CI 1.12–18.13, $P=0.034$) and V30 (OR 6.13; 95% CI 1.46–25.73, $P=0.013$) were significantly associated with ≥grade 2 RP.

Multifactorial analysis

Considering the variable covariance, GTV, ipsilateral lung V20 and total lung V20 were finally included in the multifactorial logistic regression analysis, and the results are shown in Table 5. GTV≥39 ml (OR 0.96; 95% CI 0.93–0.99, $P=0.029$) and total lung V20≥14.95% (OR 1.49; 95% CI 1.06–2.09, $P=0.022$) were the independent risk factors for the occurrence of RP independent risk factors for the development of RP.

Discussion

The emergence of third-generation EGFR TKIs has overcome resistance arising from the T790M mutation, the most common mutation in NSCLC patients with Asian EGFR gene mutations, and the therapeutic strategy of combining them with TRT has further improved mPFS and OS, but the combination of the two inevitably causes damage to normal lung tissue and increases the probability of RP. Our study retrospectively analysed 42 NSCLC patients who combined a third-generation TKIs with TRT, and the results suggested that the probability of RP was as high as 61.9% (26/42), of which 33.3% (14/42) were patients with grade≥2 RP. A previous study by Zhu Hui et al. [22] also suggested a particularly high probability of RP with osimertinib combined with TRT, analysing 11 NSCLC patients, with 63.6% experiencing grade≥2 RP and a high incidence of grade 3 and higher RP of 54.5%, but was not further analysed due to small sample size. This is the first study to report a particularly high incidence of grade 2 and higher RP in patients treated with osimertinib in combination with TRT. This is an alarming phenomenon and a reminder of the need for caution when combining TRT in patients taking osimertinib. In addition to reporting the occurrence of high RP, our study

Table 3 Relationship between clinical features and RP

Characteristic	Radiation pneumonitis (n [%]) (N=42)		*P* value	OR (95% CI)
	Yes(n=26)	No(n=16)		
Gender			0.208	2.27(0.63-8.15)
Male	11(42.3)	10(62.5)		
Female	15(57.7)	6(37.5)		
Age(year)			0.106	0.94(0.88-1.01)
＜60	15(57.7)	7(43.8)		
≥60	11(42.3)	9(56.2)		
BMI			0.576	1.06(0.86-1.32)
＜22.82	9(34.6)	9(56.3)		
≥22.82	17(65.4)	7(43.8)		
Smoking history			0.796	1.27(0.21-7.89)
Yes	22(84.6)	14(87.5)		
No	4(15.4)	2(12.5)		
Disease stage			0.860	0.80(0.07-9.61)
IIIb	2(7.7)	1(6.3)		
IV	24(92.3)	15(93.8)		
Location of the primary site			0.078	0.30(0.08-1.14)
Not included lower lob	20(76.9)	8(50.0)		
Lower lob	6(23.1)	8(50.0)		
Surgery history			0.609	0.58(0.07-4.61)
Yes	24(92.3)	14(87.5)		
No	2(7.7)	2(12.5)		
Chemotherapy history			0.777	1.27(0.25-6.59)
Yes	4(15.4)	3(18.8)		
No	22(84.6)	13(81.3)		
TKI types				
Osimertinib	16(61.5)	11(68.8)	0.794	1.16(0.39-3.44)
Aumolertinib	9(34.6)	4(25.0)		
Furmonertinib	1(3.9)	1(6.2)		

TKI tyrosine kinase inhibitor; OR odds ratio; CI confidence interval.

also identified independent risk factors associated with RP. These factors mainly included GTV, total lung V20, whereas gender, age, primary tumour stage and location, previous smoking, chemotherapy, PTV and other lung radiation dosimetric parameters could not be considered as independent risk factors for RP in our study.

Among the risk factors associated with RP, previous studies have shown that prior use of gemcitabine-containing chemotherapy regimens, primary tumour located in the lower lobes of the lung, history of diabetes mellitus, history of smoking, GTV, V20 and MLD were associated [25–27], with history of smoking being a protective factor for the development of RP, which may be related to the fact that smoking causes damage to lung tissue and decreases sensitivity to radiotherapy [28]. The above factors could not be confirmed in our study, which may be related to the sample size and patient information. In our study, we performed a multifactorial analysis of the statistically significant factors in the univariate regression analysis, and the results suggested that GTV ≥ 39 ml and

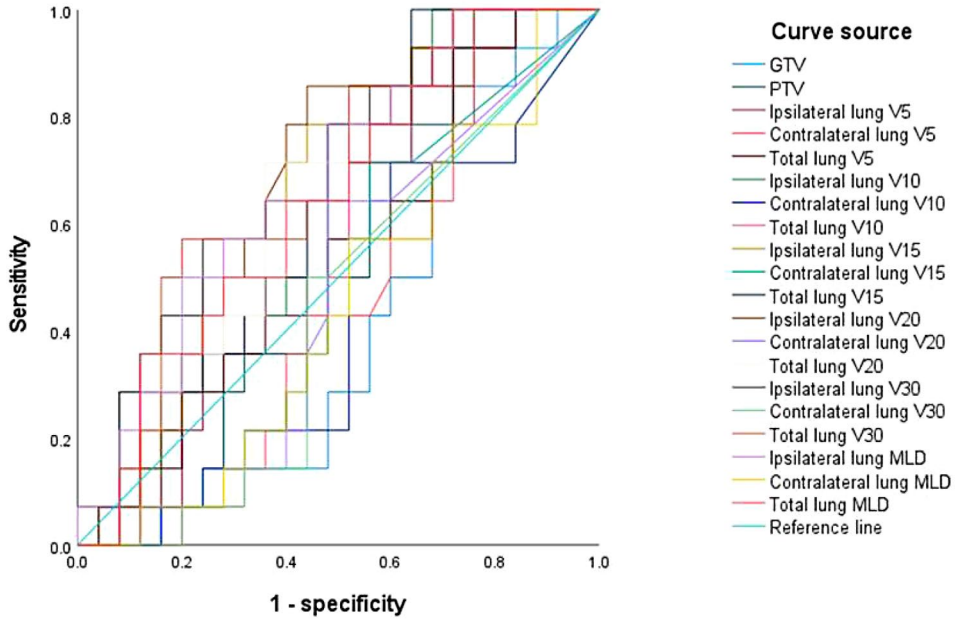

Fig. 2 Receiver operating characteristic curves of the lung dosimetry parameters for the prediction of radiation pneumonitis

Table 4 Univariate logistic regression analysis of the risk factors for grade ≥ 2 radiation pneumonitis

Factor	*P* value	OR (95% CI)
GTV	**0.047**	0.18(0.03-0.98)
PTV	0.141	0.19(0.02-1.72)
Ipsilateral lung V5	0.084	3.67(0.84-16.04)
Contralateral lung V5	0.103	0.16(0.19-1.44)
Total lung V5	0.141	5.20(0.58-46.60)
Ipsilateral lung V10	0.053	5.2(0.98-27.65)
Contralateral lung V10	0.056	0.24(0.05-1.04)
Total lung V10	0.075	7.22(0.82-63.63)
Ipsilateral lung V15	**0.036**	4.89(1.11-21.47)
Contralateral lung V15	0.141	0.19(0.02-1.72)
Total lung V15	0.999	1.3E+09
Ipsilateral lung V20	**0.015**	8.00(1.50-42.65)
Contralateral lung V20	0.074	0.28(0.07-1.13)
Total lung V20	**0.034**	4.50(1.12-18.13)
Ipsilateral lung V30	**0.025**	4.89(1.22-19.65)
Contralateral lung V30	0.053	0.19(0.04-1.02)
Total lung V30	**0.013**	6.13(1.46-25.73)
Ipsilateral lung MLD	0.056	4.23(0.97-18.53)
Contralateral lung MLD	0.141	0.19(0.02-1.72)
Total lung MLD	0.999	1.1E+09

GTV gross tumor volume; PTV planning target volume; MLD median lung dose; OR odds ratio; CI confidence interval.

Table 5 Multivariate logistic regression was used to analyze the risk factors of radiation pneumonitis

Factor	*P* value	OR (95% CI)
GTV (ml)	**0.029**	0.96(0.93-0.99)
<39		
≥39		
Ipsilateral lung V20(%)	0.428	1.04(0.94-1.16)
<28.91		
≥28.91		
Total lung V20(%)	**0.022**	1.49(1.06-2.09)
<14.95		
≥14.95		

GTV gross tumor volume; OR odds ratio; CI confidence interval.

total lung V20 ≥ 14.95% were independent risk factors for RP. This is different from the study by Zhu Hui's team on the risk factors for RP occurring with aumolertinib combined with TRT [23], in which GTV ≥ 21 ml was an independent predictor of RP. Although we have different values for GTV cut-offs, they all suggest that there is a non-negligible and important role of GTV in predicting RP, and further studies are needed to determine the specific dose range.

The incidence of RP increased significantly after the combination of TKIs and TRT, and the specific mechanism is not yet clear. The pathogenesis of RP involves a combination of factors such as the overproduction of reactive oxygen species (ROS), the release of inflammatory cytokines and mediators, the proliferation of fibroblasts and the deposition of extracellular matrix [29]. First, by targeting and inhibiting EGFR and its signalling pathway in lung cancer cells, TKIs inhibit tumour cell proliferation and growth. At the same time, it causes alveolar and bronchial epithelial damage and chronic inflammation, both of which stimulate fibroblast migration, proliferation and extracellular matrix production, leading to lung fibrosis. On the other hand, it reduces Clara cell secretory protein (CCSP) and affects Clara cells, reducing the inhibitory effect on inflammatory factors and promoting the development of pneumonia [30]. Secondly, TKIs can act as sensitising agents for radiotherapy, and TKI-irradiated tissues are exposed to direct damage including base deletions, DNA single- and double-strand breaks [31]. On the other hand, indirect damage is caused by ROS activation. Finally, DNA damage and ROS activation together activate cell signalling factors and pathways, and damage-associated cytokines such as transforming growth factor-β, platelet-derived growth factor and interleukin are released from cells, recruiting more immune effector cells, accumulating lung tissue damage and promoting tissue remodelling. Triggered by cell adhesion molecules, immune cells like neutrophils and macrophages further release IL-3, IL-6, IL-7, TNF-α and so on, promoting the inflammatory response and ultimately leading to the development of RP.

Our study was limited by the characteristics of a retrospective study with missing data, resulting in a small final sample size for inclusion and a short follow-up period. Increasing the sample size allows better analysis of the relevant factors, while taking into account the covariance effects of some factors to improve predictive performance. Meanwhile, as many predictive factors as possible were found to further construct the prediction model. Although third-generation EGFR TKIs have been used as a first-line treatment option for NSCLC patients with EGFR gene mutations, significantly prolonging survival, and combined with TRT is currently a clinically recommended treatment strategy, the increase in the incidence of RP suggests that further evaluation of the long-term clinical benefit of the combination strategy is still needed. Follow-up of this study is ongoing and the sample size continues to increase. In the future, we will carry out prospective studies to explore more new prediction factors (such as biological markers, TKI-TRT interval, TKI blood concentration, and other factors), and even incorporate dosimetry and imaging genomics to build prediction models together to provide a better solution and reference value.

Conclusion

In conclusion, our study comprehensively reports a particularly high incidence of RP in patients with NSCLC treated with the combination of a third-generation EGFR TKIs and TRT. Independent predictors of the occurrence of RP were GTV and total lung V20. Despite the significant increase in the incidence of RP, the strategy of combination therapy significantly prolonged survival while the occurrence of RP was within acceptable limits. TRT

is one of the important treatments for patients with thoracic progression, and the role of combination TRT therapy should not be negated because of the incidence of RP. Therefore, future studies should continue to explore the appropriate timing and dose of combined TRT and the development of pulmonary radiation dosimetry parameters without compromising clinical efficacy.

Abbreviations

NSCLC	Non-small cell lung cancer
EGFR-TKI	Epidermal growth factor receptor tyrosine kinase inhibitor
TRT	Thoracic radiotherapy
RP	Radiation pneumonia
CT	Computed tomography
mPFS	Median progression-free survival
OS	Overall survival
ECOG	Eastern Cooperative Oncology Group
DVH	Dose-volume histogram
VMAT	Volumetric modulated arc therapy
IMRT	Intensity-modulated radiotherapy
TOMO	Tomotherapy
3D-CRT	Three-dimensional conformal radiotherapy
GTV	Gross tumor volume
PTV	Planning target volume
MLD	Mean lung dose
ROC	Receiver operating characteristic curve
OR	Odds ratio
CI	Confidence interval
ROS	Reactive Oxygen Species
CCSP	Clara Cell Secretory Protein

Acknowledgements
Not applicable.

Author contributions
Nan Zhao and Yanyang Wang designed the study. Nan Zhao and Liang Xiong counted the statistics and drafted the manuscript. Xuehong Bai, Wenyan Pan, and Ping Hai diagnosed radiation pneumonitis. Hongqiang Ye and Ting Zhao determined the radiation dose and provided the data. Kai Cui and Rong Ma analysis of data. All authors read and approved the final manuscript.

Funding
This work was supported by the Ningxia Health Research Project (2022-NWKY-063).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Review Committee of the General Hospital of Ningxia Medical University and was performed in accordance with the Declaration of Helsinki.

Consent for publication
This is a retrospective study that has no need to receive patient informed consent.

Competing interests
The authors declare no competing interests.

Received: 12 March 2025 / Accepted: 24 April 2025
Published online: 09 May 2025

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin. 2021;71(1):7–33.
2. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. Nature. 2018;553(7689):446–54.
3. Forde PM, Ettinger DS. Targeted therapy for non-small-cell lung cancer: past, present and future. Expert Rev Anticancer Ther. 2013;13(6):745–58.
4. Andrews Wright NM, Goss GD. Third-generation epidermal growth factor receptor tyrosine kinase inhibitors for the treatment of non-small cell lung cancer. Transl Lung Cancer Res. 2019;8(Suppl 3):S247–64.
5. He J, Huang Z, Han L, Gong Y, Xie C. Mechanisms and management of 3rdgeneration EGFRTKI resistance in advanced nonsmall cell lung cancer (Review). Int J Oncol. 2021;59(5):90.
6. Lamb YN, Osimertinib. A review in previously untreated, EGFR Mutation-Positive, advanced NSCLC. Target Oncol. 2021;16(5):687–95.
7. Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, et al. Cervical cancer, version 3.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2019;17(1):64–84.
8. Lu S, Wang Q, Zhang G, Dong X, Yang CT, Song Y, et al. Efficacy of aumolertinib (HS-10296) in patients with advanced EGFR T790M + NSCLC: updated Post-National medical products administration approval results from the APOLLO registrational trial. J Thorac Oncol. 2022;17(3):411–22.
9. Akamatsu H, Toi Y, Hayashi H, Fujimoto D, Tachihara M, Furuya N, et al. Efficacy of osimertinib plus bevacizumab vs osimertinib in patients with EGFR T790M-Mutated Non-Small cell lung Cancer previously treated with epidermal growth factor Receptor-Tyrosine kinase inhibitor: West Japan oncology group 8715L phase 2 randomized clinical trial. JAMA Oncol. 2021;7(3):386–94.
10. Park S, Ku BM, Jung HA, Sun JM, Ahn JS, Lee SH, et al. EGFR C797S as a resistance mechanism of lazertinib in Non-small cell lung Cancer with EGFR T790M mutation. Cancer Res Treat. 2020;52(4):1288–90.
11. Wang Y, Tian P, Xia L, Li L, Han R, Zhu M, et al. The clinical efficacy of combinatorial therapy of EGFR-TKI and Crizotinib in overcoming MET amplification-mediated resistance from prior EGFR-TKI therapy. Lung Cancer. 2020;146:165–73.
12. Friedlaender A, Subbiah V, Russo A, Banna GL, Malapelle U, Rolfo C, et al. EGFR and HER2 exon 20 insertions in solid tumours: from biology to treatment. Nat Rev Clin Oncol. 2022;19(1):51–69.
13. Zhang S, Chen Z, Shi P, Fan S, He Y, Wang Q, et al. Downregulation of death receptor 4 is tightly associated with positive response of EGFR mutant lung cancer to EGFR-targeted therapy and improved prognosis. Theranostics. 2021;11(8):3964–80.
14. Hsu CC, Liao BC, Liao WY, Markovets A, Stetson D, Thress K, et al. Exon 16-Skipping HER2 as a novel mechanism of osimertinib resistance in EGFR L858R/T790M-Positive Non-Small cell lung Cancer. J Thorac Oncol. 2020;15(1):50–61.
15. Vicencio JM, Evans R, Green R, An Z, Deng J, Treacy C, et al. Osimertinib and anti-HER3 combination therapy engages immune dependent tumor toxicity via STING activation in trans. Cell Death Dis. 2022;13(3):274.
16. Lee PH, Huang YH, Lin H, Hsu KH, Chen KC, Tseng JS, et al. Histological transformation after acquired resistance to the Third-Generation EGFR-TKI in patients with advanced *EGFR*-Mutant lung adenocarcinoma. Med (Kaunas). 2022;58(7):908.
17. Stegelmeier P, Dawson JA, Wallace M, Esebua M. Osimertinib resistance via histologic transformation from Non-small cell lung carcinoma to carcinosarcoma. Cureus. 2024;16(4):e59293.
18. Tang Y, Xia B, Xie R, Xu X, Zhang M, Wu K, et al. Timing in combination with radiotherapy and patterns of disease progression in non-small cell lung cancer treated with EGFR-TKI. Lung Cancer. 2020;140:65–70.
19. Wang N, Wang L, Meng X, Wang J, Zhu L, Liu C, et al. Osimertinib (AZD9291) increases radiosensitivity in EGFR T790M nonsmall cell lung cancer. Oncol Rep. 2019;41(1):77–86.
20. Peng P, Gong J, Zhang Y, Zhou S, Li Y, Han G, et al. EGFR-TKIs plus stereotactic body radiation therapy (SBRT) for stage IV Non-small cell lung cancer (NSCLC): A prospective, multicenter, randomized, controlled phase II study. Radiother Oncol. 2023;184:109681.
21. Sanchis-Borja M, Parrot A, Sroussi D, Rivin Del Campo E, Fallet V, Cadranel J. Dramatic radiation recall pneumonitis induced by osimertinib after palliative thoracic radiotherapy for lung Cancer. J Thorac Oncol. 2019;14(10):e224–6.
22. Jia W, Guo H, Jing W, Jing X, Li J, Wang M, et al. An especially high rate of radiation pneumonitis observed in patients treated with thoracic radiotherapy and simultaneous osimertinib. Radiother Oncol. 2020;152:96–100.

23. Yin H, Jia W, Yu J, Zhu H. Radiation pneumonitis after concurrent aumolertinib and thoracic radiotherapy in EGFR-mutant non-small cell lung cancer patients. BMC Cancer. 2024;24(1):197.
24. U.S.Department of Health and Human Services.Common terminology criteria for adverse events(CTCAE)version 5.0[S/OL]. 2017:137–138.
25. Han S, Gu F, Lin G, Sun X, Wang Y, Wang Z, et al. Analysis of clinical and dosimetric factors influencing Radiation-Induced lung injury in patients with lung Cancer. J Cancer. 2015;6(11):1172–8.
26. Shiraishi S, Sugimoto M, Tokuuye K. Salivary metabolites as novel independent predictors of radiation pneumonitis. J Cancer Res Clin Oncol. 2023;149(19):17559–66.
27. Du L, Ma N, Dai X, Yu W, Huang X, Xu S, et al. Precise prediction of the radiation pneumonitis in lung cancer: an explorative preliminary mathematical model using genotype information. J Cancer. 2020;11(8):2329–38.
28. Qiu F, Liang CL, Liu H, Zeng YQ, Hou S, Huang S, et al. Impacts of cigarette smoking on immune responsiveness: up and down or upside down? Oncotarget. 2017;8(1):268–84.
29. Chang S, Lv J, Wang X, Su J, Bian C, Zheng Z, et al. Pathogenic mechanisms and latest therapeutic approaches for radiation-induced lung injury: A narrative review. Crit Rev Oncol Hematol. 2024;202:104461.
30. Yamamoto Y, Saita T, Kataoka H, Sogawa R, Kimura S, Kimura S, et al. Localization of sites of osimertinib action in rat intestine, skin, and lung by immunohistochemistry. Acta Histochem Cytochem. 2023;56(6):145–51.
31. Giuranno L, Ient J, De Ruysscher D, Vooijs MA. Radiation-Induced lung injury (RILI). Front Oncol. 2019;9:877.

Publisher's note