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Impact of Thoracic Radiotherapy Timing on Resistance and Survival in Patients with Advanced EGFR-Mutant Lung Adenocarcinoma Treated with EGFR Tyrosine Kinase Inhibitors

Chenran Zhao*
Shandong First Medical University, Jinan 250000, Shandong, China

Author to whom correspondence should be addressed.

Abstract: *Objective:* We evaluated whether thoracic radiotherapy before acquired epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) resistance improves survival in stage IV EGFR-mutant lung adenocarcinoma. *Methods:* We reviewed 182 patients with stage IV EGFR-mutant lung adenocarcinoma who received EGFR-TKIs and thoracic radiotherapy at one cancer center. We assigned 120 patients to a pre-resistance radiotherapy group and 62 patients to a post-resistance radiotherapy group according to radiotherapy timing. Overall survival (OS) and thoracic progression-free survival (tPFS) served as co-primary endpoints. Metastatic progression-free survival (mPFS) served as a secondary endpoint. We used Kaplan-Meier analysis, log-rank testing, Cox regression, and chi-square testing. *Results:* Median OS was 59.4 months and 38.8 months, respectively (log-rank test $P = 0.0489$, hazard ratio [HR]: 0.6965, 95% CI: 0.4678–0.9037), and median tPFS was 33.9 months and 16.1 months, respectively (log-rank test $P = 0.0005$, HR: 0.5334, 95% CI: 0.3487–0.8161). The mPFS was 34.8 months and 26.9 months, respectively (log-rank test $P = 0.0615$, HR: 0.7985, 95% CI: 0.5266–1.134). The results of univariate and multivariate Cox regression analysis showed that timing of thoracic radiotherapy ($P = 0.048$) was an independent indicator of improved survival outcomes in patients with EGFR-mutant lung adenocarcinoma. *Conclusion:* Thoracic radiotherapy before acquired resistance correlated with longer survival and stronger thoracic disease control in advanced EGFR-mutant lung adenocarcinoma.

Keywords: Advanced lung adenocarcinoma; EGFR-TKIs; Thoracic radiotherapy; Overall survival

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1. Introduction

Lung adenocarcinoma remains the most common histologic subtype of non-small cell lung cancer, and epidermal growth factor receptor (EGFR) mutation has defined a major therapeutic subgroup within advanced disease. Targeted therapy has changed first-line treatment in this population because sensitizing EGFR mutations predict high response rates and longer progression-free survival with EGFR-tyrosine kinase inhibitors (TKIs) than with cytotoxic chemotherapy. Even so, durable control remains difficult because most tumors develop acquired resistance during continuous treatment, and thoracic

progression often drives treatment failure in daily practice [1].

The chest remains a major reservoir of residual disease after initial response to EGFR-TKIs. Persistent primary tumor burden and thoracic nodal disease can support clonal evolution, recurrent symptoms, and later disseminated progression. This clinical pattern has increased interest in local thoracic treatment during targeted therapy. Thoracic radiotherapy can improve local control, reduce viable tumor burden, and extend the duration of benefit from systemic treatment in selected patients. The key clinical question concerns timing. Many clinicians defer thoracic radiotherapy until resistance becomes evident, yet earlier treatment during the response phase may produce longer control of intrathoracic disease and better survival outcomes [2].

2. Materials and methods

A retrospective cohort study was performed at our hospital to evaluate the clinical significance of thoracic radiotherapy timing in patients with advanced EGFR-mutant lung adenocarcinoma treated with EGFR-TKIs. The institutional ethics committee approved the study protocol. The hospital archive identified patients with advanced non-small cell lung cancer who had received treatment during the study period. All available records underwent screening, and the analysis retained only those cases that satisfied every prespecified eligibility criterion. Eligible patients had pathologically confirmed primary lung adenocarcinoma, a documented EGFR mutation in exon 18, 19, 20, or 21, complete clinical and treatment information, prior exposure to EGFR-TKIs, and thoracic radiotherapy administered during systemic therapy. The exclusion criteria included the presence of another primary malignancy and the absence of objective thoracic evaluation by enhanced computed tomography, magnetic resonance imaging, or cytologic examination. The final cohort comprised 182 patients.

The clinical team divided the cohort into two groups according to the timing of thoracic radiotherapy in relation to acquired EGFR-TKIs resistance. The pre-resistance group included 120 patients who received thoracic radiotherapy before resistance emerged, whereas the post-resistance group included 62 patients who underwent thoracic radiotherapy after resistance developed. The institutional record defined resistance on the basis of radiographic or clinical progression after a preceding period of disease control during EGFR-TKIs treatment. The targeted agents used in this cohort included gefitinib, erlotinib, and icotinib.

The investigators extracted demographic, molecular, treatment, and outcome variables from the electronic medical record system. These variables included sex, age at diagnosis, smoking history, EGFR mutation subtype, first-line targeted treatment status, chemotherapy exposure before thoracic radiotherapy, thoracic radiotherapy timing, survival status, radiotherapy fraction size, total radiation dose, and progression outcomes. Thoracic radiotherapy targeted the primary lung lesion and thoracic metastatic lymph nodes in all patients. Fraction size ranged from 2.0 Gy to 5.5 Gy, and total dose ranged from 27 Gy to 75 Gy. Among the 182 patients, 96 were younger than 55 years and 86 were 55 years or older. Women accounted for 110 cases, and never-smokers accounted for 141 cases. Common sensitizing EGFR mutations predominated, with exon 19 deletion or exon 21 L858R mutation detected in 176 patients.

Overall survival was defined as the interval from diagnosis to death from any cause or the last follow-up visit. Thoracic progression-free survival was defined as the interval from targeted treatment initiation or thoracic radiotherapy to thoracic progression or death. Metastatic progression-free survival was defined as the interval from treatment initiation to progression at distant metastatic sites. Overall survival (OS) and thoracic progression-free survival **(**tPFS**)** served as co-primary endpoints, while metastatic progression-free survival **(**mPFS**)** served as a secondary endpoint. Categorical variables were summarized as counts and percentages. Chi-square testing described categorical distributions in the available cohort-level data. The Kaplan-Meier method generated survival curves, and the log-rank test compared survival differences. Cox proportional hazards regression evaluated prognostic factors for overall survival. All statistical analyses used SPSS version 26.0, and statistical significance was set at a *P* value below 0.05.

3. Results

Table 1 presents the baseline clinicopathologic and treatment features of the 182 enrolled patients. The cohort showed the typical profile of EGFR-mutant advanced lung adenocarcinoma, with female predominance, a high proportion of never-smokers, and frequent common sensitizing mutations. Median age at diagnosis was 53.5 years. Thoracic radiotherapy was delivered before acquired resistance in 120 patients and after resistance in 62 patients. At the last follow-up, 121 patients had died.

Median overall survival for the whole cohort was 49.4 months, and median thoracic progression-free survival was 18.3 months. Patients who received thoracic radiotherapy before acquiring resistance achieved longer overall survival than those treated after resistance, with median values of 59.4 and 38.8 months. Thoracic progression-free survival also favored the pre-resistance group, with median values of 33.9 and 16.1 months. Median metastatic progression-free survival was 34.8 months in the pre-resistance group and 26.9 months in the post-resistance group. **Table 2** shows univariable and multivariable analyses of covariates associated with OS.

Table 1. Chi-square analysis of categorical characteristics

Characteristics	Before resistance (n = 120)	After resistance (n = 62)	P value
Age, years			
> 55	59(49.2)	27(43.5)	0.4718
≤ 55	61(50.8)	35(56.5)	
Gender			
Male	72(60.0)	38(61.3)	0.8660
Female	48(40.0)	24(38.7)	
Smoking status			
No	92(76.6)	49(79.1)	0.7173
Yes	28(23.4)	13(20.9)	
EGFR mutation			
Exon 19	59(49.2)	29(46.7)	0.1644
Exon 21	55(45.8)	33(53.3)	
Other	6(5.0)	0(0.0)	
Systemic therapy			
First-line EGFR-TKIs therapy	41(34.2)	33(53.3)	0.0631
Second-line EGFR-TKIs therapy	79(65.8)	29(46.7)	
Chemotherapy before thoracic radiotherapy			
Yes	88(73.4)	43(69.3)	0.5711
No	32(26.6)	19(30.7)	
Brain metastasis			
Yes	74(61.6)	44(70.9)	0.2130
No	46(38.4)	18(29.1)	

Table 2. Univariable and multivariable analyses of covariates associated with OS

Variable	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Sex	1.041	0.722 to 1.502	0.829			
Age	0.905	0.632 to 1.295	0.584			
Smoking history	1.121	0.729 to 1.724	0.603			

Variable	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
EGFR mutation type	0.857	0.349 to 2.106	0.737			
First-line EGFR-TKIs treatment	0.920	0.632 to 1.341	0.665			
Chemotherapy before thoracic radiotherapy	1.123	0.748 to 1.685	0.575			
Thoracic radiotherapy timing	0.685	0.470 to 1.001	0.050	0.669	0.449 to 0.997	0.048

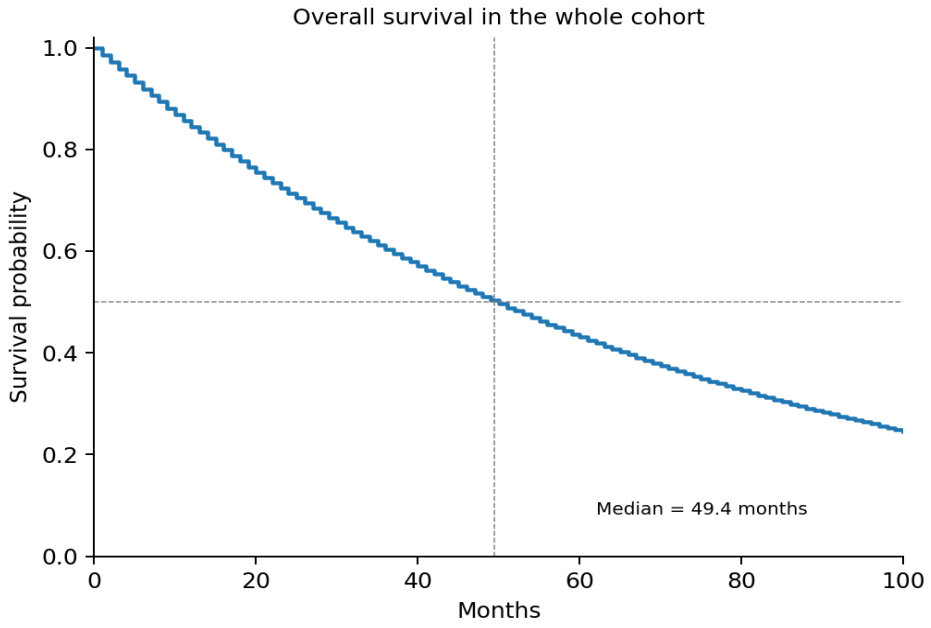

Figure 1. Overall survival in the whole cohort

Kaplan-Meier display reconstructed from the reported cohort median overall survival of 49.4 months (**Figure 1**).

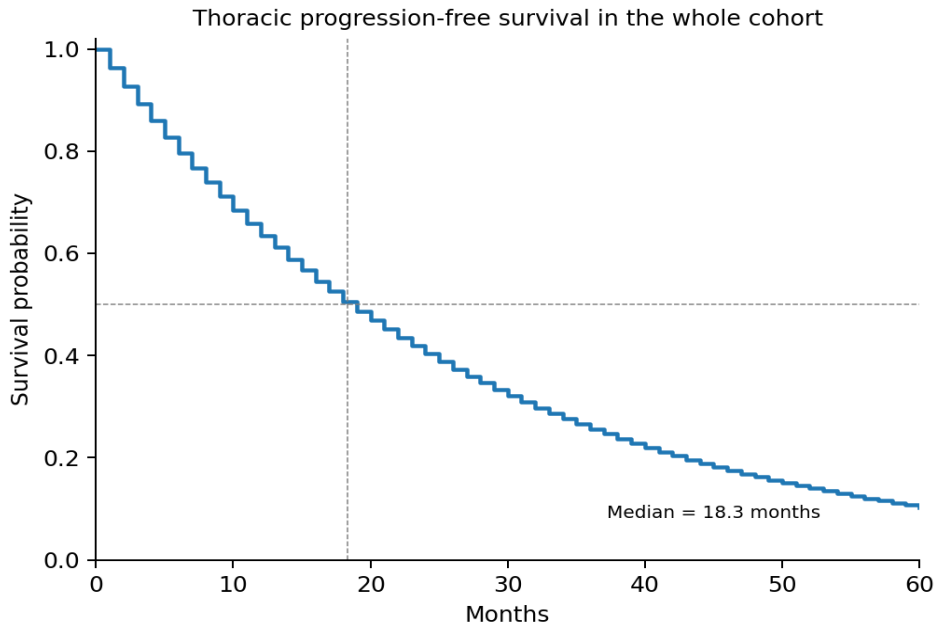

Figure 2. Thoracic progression-free survival in the whole cohort

Kaplan-Meier display reconstructed from the reported cohort median tPFS of 18.3 months (**Figure 2**).

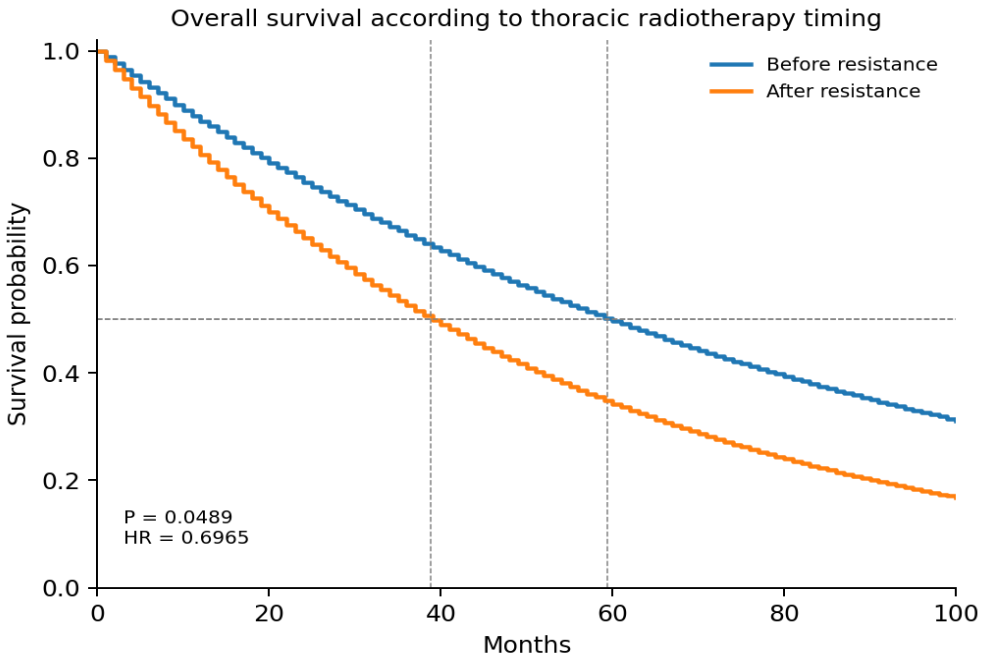

Figure 3. Overall survival according to thoracic radiotherapy timing

Kaplan-Meier display reconstructed from the reported group medians, hazard ratio, and log-rank *P* value (**Figure 3**).

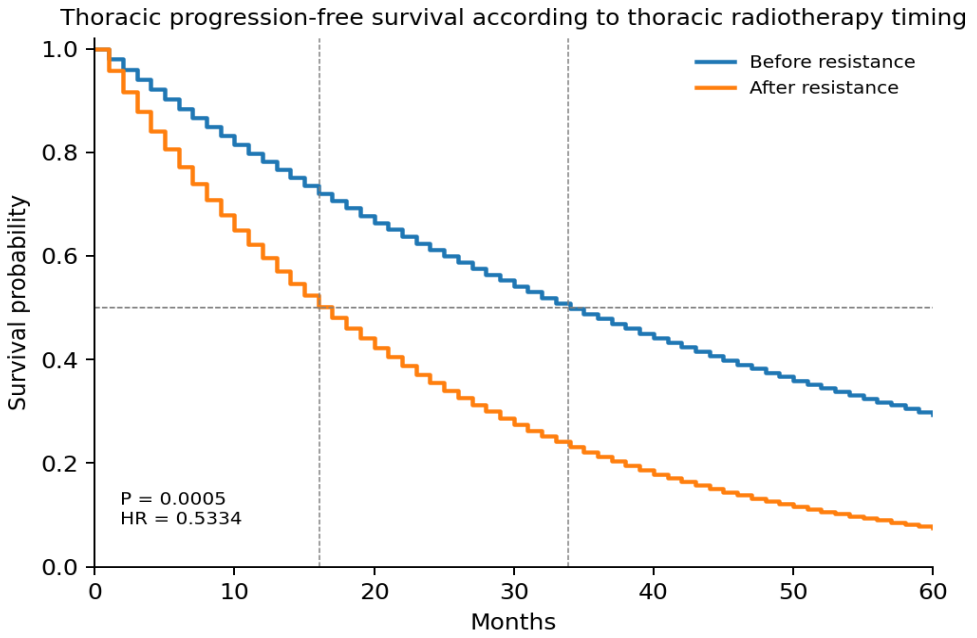

Figure 4. Thoracic progression-free survival according to thoracic radiotherapy timing

Kaplan-Meier display reconstructed from the reported group medians, hazard ratio, and log-rank *P* value (**Figure 4**).

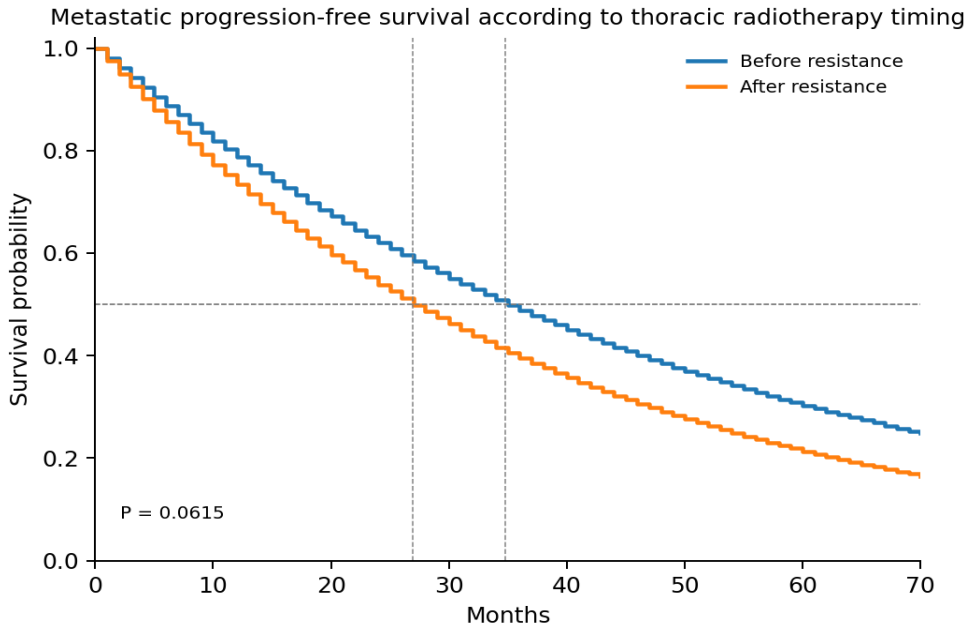

Figure 5. Metastatic progression-free survival according to thoracic radiotherapy timing

Kaplan-Meier display reconstructed from the reported group medians and log-rank *P* value (**Figure 5**).

4. Discussion

The present analysis shows that thoracic radiotherapy timing carries major clinical importance in stage IV EGFR-mutant lung adenocarcinoma treated with EGFR-TKIs. Patients who received thoracic radiotherapy before acquiring resistance achieved longer overall survival and markedly longer thoracic progression-free survival than patients who received thoracic radiotherapy after resistance. The multivariate model retained thoracic radiotherapy timing as an independent prognostic factor, which strengthens the clinical credibility of the observed timing effect. The effect size also matters in practical terms. A 20.6-month difference in median overall survival and a 17.8-month difference in median thoracic progression-free survival represent changes that clinicians and patients can perceive directly in disease course, treatment continuity, and symptom control.

The biological context supports these findings. EGFR-mutant tumors often respond rapidly to targeted therapy, yet residual thoracic disease usually persists even when radiographic response appears substantial. Residual primary lesions and thoracic nodal deposits can maintain a pool of viable tumor cells under selective drug pressure, which can accelerate clonal diversification and later overt resistance. Reviews of advanced EGFR-mutant lung adenocarcinoma continue to describe acquired resistance as the central barrier to durable disease control, even in molecularly selected populations with initially high response rates [3]. Early thoracic radiotherapy reduces residual thoracic tumor burden during a stage when local disease remains more spatially confined and more biologically linked to the original drug-sensitive clone.

The current results also fit the therapeutic history of EGFR-TKIs. Landmark randomized evidence established targeted therapy as the preferred initial treatment for mutation-positive advanced disease because it improved response and progression-free survival over chemotherapy [4]. That success, however, exposed a second challenge. Once the TKIs control the systemic component of the disease, the chest often becomes the most persistent site of tumor burden. Thoracic progression may then drive symptoms, trigger treatment change, and seed future dissemination. In that context, thoracic

radiotherapy can function not as a salvage maneuver of last resort but as a planned local consolidation strategy that preserves the period of benefit from targeted therapy.

Clinical pattern-of-failure research supports this model. Prior work in metastatic EGFR-mutant lung cancer identified the thorax as a frequent site of progression during TKIs treatment and highlighted the value of consolidative local therapy for carefully selected patients [5]. The same principle appears in timing-focused observational studies. When clinicians integrated radiotherapy during treatment response rather than after broader resistant progression, long-term efficacy improved, which suggests that treatment timing changes outcome rather than merely reflecting outcome [6]. The current dataset extends that observation to a cohort in which thoracic radiotherapy targeted the primary lesion and thoracic metastatic lymph nodes throughout the study population.

The strong separation in thoracic progression-free survival deserves particular emphasis. Median thoracic progression-free survival measured 33.9 months in the pre-resistance group and 16.1 months in the post-resistance group, with a hazard ratio of 0.5334. This result suggests that the dominant therapeutic gain from earlier radiotherapy lies in local thoracic control. The chest remains the compartment where targeted therapy, imaging response, and local failure intersect most visibly. Once resistance emerges, thoracic lesions often enlarge in a biologically heterogeneous environment that includes resistant subclones, altered microenvironmental signaling, and larger effective target volumes. Radiotherapy delivered after that point may still palliate or control focal progression, but it no longer acts within the same therapeutic window as radiotherapy delivered during the response phase.

Published studies of local ablative therapy and upfront thoracic radiotherapy strengthen the interpretation of the present findings. Consolidative local ablative therapy has prolonged survival in patients with synchronous oligometastatic non-small cell lung cancer harboring EGFR activating mutations during first-line EGFR-TKIs treatment [7]. Upfront thoracic radiotherapy directed at the primary lesion has also improved outcomes in stage IV disease with EGFR mutations [8]. These reports do not match the current cohort in every detail, yet they point in the same direction. Local thoracic disease matters, and early local control can translate into longer survival when systemic targeted therapy has already established disease sensitivity.

The metastatic progression-free survival result adds an important nuance. The pre-resistance group showed a longer median metastatic progression-free survival than the post-resistance group, but the comparison did not reach formal statistical significance. This pattern indicates that thoracic radiotherapy exerts its most direct influence on intrathoracic disease. The effect on distant metastatic evolution likely depends on several additional variables, including baseline metastatic burden, timing of clonal escape outside the thorax, and duration of continued EGFR-TKIs benefit after local treatment. Even so, the consistent numerical advantage across all three time-to-event endpoints supports the overall coherence of the dataset. The absence of statistical significance for metastatic progression-free survival does not weaken the more robust signals for overall survival and thoracic progression-free survival.

Recent reports from the third-generation EGFR-TKIs era reinforce the current relevance of timing. Combined thoracic radiotherapy and first-line third-generation EGFR-TKIs have improved progression-free survival in oligo-organ metastatic disease, and radiotherapy timing remained an important determinant of outcome [9]. Modern drugs can alter resistance mechanisms and extend systemic control, but they do not remove the clinical importance of persistent thoracic disease.

Several practical implications arise from these findings. Clinicians should evaluate thoracic disease burden early during EGFR-TKIs response and should not defer local thoracic treatment automatically until overt resistant progression occurs. Multidisciplinary planning should treat the primary thoracic lesion and involved thoracic lymph nodes as active determinants of long-term outcome. Future protocols should include treatment timing as a formal study variable.

5. Conclusion

Thoracic radiotherapy before acquired EGFR-TKIs resistance correlated with longer overall survival and longer thoracic progression-free survival in stage IV EGFR-mutant lung adenocarcinoma. The timing of thoracic radiotherapy remained

an independent prognostic factor in multivariate analysis. Early local thoracic intervention therefore merits consideration during the responsive phase of targeted treatment.

Disclosure statement

The author declares no conflict of interest.

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