

# Optimal timing of thoracic radiotherapy with osimertinib in unresectable EGFR-mutant non-small cell lung cancer

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**Abstract.** Osimertinib is standard first-line therapy for EGFR-mutant non-small cell lung cancer (NSCLC); however, the optimal timing of combined thoracic radiotherapy (TRT) remains unclear. The aim of the present study was to investigate the relationship between the interval from osimertinib treatment to TRT interval and the survival outcomes, defining an optimal therapeutic window for unresectable EGFR-mutant NSCLC. Data from 175 patients with stage IIIB/IV EGFR-mutant NSCLC receiving first-line osimertinib and consolidation TRT were retrospectively analyzed. Cox regression and restricted cubic spline (RCS) models, inverse probability of treatment weighting, and left-truncated and landmark analyses were performed. At a median follow-up time of 25.3 months, each 1-day delay in the osimertinib-to-TRT interval was identified as an independent adverse prognostic factor for locoregional progression-free survival [hazard ratio (HR), 1.02; 95% confidence interval (CI), 1.01-1.02;  $P<0.001$ ], progression-free survival (HR, 1.01; 95% CI, 1.01-1.02;  $P<0.001$ ), and overall survival (HR, 1.02; 95% CI, 1.01-1.02;  $P<0.001$ ). The RCS model revealed a significant non-linear J-shaped association (non-linear  $P<0.05$ ), with risk peaking between 40 and 102 days. All sensitivity analyses, including inverse probability of treatment weighting, left-truncated immortal time bias adjustment, 3/6/12-month landmark analyses, and osimertinib response adjustment, yielded consistent effect estimates. These findings indicate that the interval between osimertinib and TRT initiation is an independent prognostic factor for EGFR-mutant NSCLC, with a non-linear J-shaped association with survival. TRT initiation

within 40 days of osimertinib commencement confers optimal benefit, providing evidence-based guidance for clinical treatment decision-making.

## Introduction

Non-small cell lung cancer (NSCLC) accounts for 85% of all confirmed lung cancer cases in the United States (1). NSCLC is difficult to detect in the early stages and has a high degree of malignancy and invasiveness. Therefore, the majority of patients with lung cancer are diagnosed with an already locally advanced stage or metastatic lesions at first presentation. Although surgery, radiotherapy (RT), chemotherapy, and other treatments can prolong the survival time of patients with late-stage disease, the overall survival rate of NSCLC is still poor. For patients with stage IV NSCLC in the United States, the 1-year survival rate was 25.1%, with a median overall survival of only 8.2 months (2).

EGFR mutation is one of the most common types of gene mutations in NSCLC. Patients with advanced or metastatic NSCLC carrying EGFR gene mutations (such as exon 19 deletion or exon 21 point mutation) exhibit high sensitivity to EGFR tyrosine kinase inhibitors (TKIs) (3). Osimertinib is a representative third-generation EGFR-TKI that can exert marked inhibitory effects on tumor cell proliferation, invasion, and metastasis by effectively inhibiting mutant EGFR activation (3,4). Osimertinib irreversibly binds to cysteine residue 797 at the ATP binding site of EGFR. Compared with gefitinib and erlotinib, osimertinib exhibits marked antitumor activity (4) and has the ability to overcome T790M mutation-mediated drug resistance, whilst moderately inhibiting the abnormal activation state of human epidermal growth factor receptor 2 (5). In addition, osimertinib addresses the toxic side effects of second-generation EGFR-TKIs.

Thoracic RT (TRT) is an indispensable component of multimodal therapy for patients with advanced NSCLC, particularly for achieving local tumor control. Accumulating evidence suggests that the combination of local TRT with systemic therapy may be a promising strategy for patients with oligo-metastatic or oligo-progressive disease (6,7), as it may eliminate resistant tumor cells or control dominant local lesions, thereby prolonging the time to systemic treatment failure. Pre-emptive TRT before the onset of disease progression has also been proposed as an effective strategy to

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counteract resistance, especially that mediated by the T790M mutation (8). Furthermore, TKIs possess a radiosensitizing effect, which can enhance the antitumor efficacy of TRT and mitigate secondary drug resistance (9). However, the optimal timing and the sequencing of TRT combined with EGFR-TKIs remain subjects of considerable debate. Whilst concurrent administration may offer enhanced antitumor effects, it also carries an increased risk of severe adverse events, such as radiation pneumonitis or esophagitis, which can lead to treatment interruption. By contrast, a sequential approach may reduce toxicity, but risks compromising local control by delaying intervention (10). In addition, the majority of existing studies on this combined modality have focused on first- or second-generation EGFR-TKIs (11). Despite the existence of studies reporting improvements in progression-free survival (PFS) and overall survival (OS) as a result of the combination of TRT and earlier-generation EGFR-TKI (12), there remains a distinct lack of evidence for guiding the optimal timing of TRT in the context of third-generation osimertinib therapy. This knowledge gap highlights the need for a comprehensive investigation into the relationship between different TRT intervals and the prognosis of patients receiving osimertinib.

The aim of the present study was to investigate the relationship between different TRT intervals and the prognosis of patients with advanced lung adenocarcinoma receiving osimertinib, while exploring the optimal treatment intervals and beneficiary population for TRT.

## Patients and methods

**Study design.** The present study was a single-center, retrospective study performed at The Fourth Affiliated Hospital of Guangxi Medical University (Liuzhou, China). The study protocol was approved by the Institutional Ethics Committee of The Fourth Affiliated Hospital of Guangxi Medical University (approval no. KY2024162). All analyses were conducted after patient de-identification, ensuring that there was no interference with therapeutic management. In the present study, patients with stage IIIB and IV NSCLC who received osimertinib treatment between January 2018 and December 2022 were included. All these patients had pathologically confirmed EGFR gene mutations (exon 19 deletions or exon 21 L858R point mutations) and were evaluated as unresectable by a multidisciplinary team. All patients received osimertinib (80 mg once daily) as a first-line therapy until disease progression or treatment intolerance necessitated a regimen change.

Inclusion criteria were as follows: i) Age >18 years; ii) Eastern Cooperative Oncology Group (ECOG) performance status of  $\leq 2$  (13); iii) receipt of TRT for consolidation therapy; iv) stage IIIB and IV NSCLC according to the American Joint Committee on Cancer 8th edition staging system (14); v) presence of measurable lesions and assessable disease status based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (15); and vi) complete follow-up data.

Exclusion criteria were as follows: i) Missing clinical or imaging data; ii) presence of other primary malignancies; iii) pathologically or cytologically confirmed non-adenocarcinoma histology; iv) lack of an EGFR mutation; v) patients who did not receive both targeted therapy and

RT; vi) succumbing to a non-oncological cause; vii) brain metastasis at initial diagnosis; viii) performing radiation therapy first, followed by drug therapy; and ix) patients with an interruption of osimertinib treatment for >7 days prior to stereotactic RT. Clinical and follow-up data were collected from electronic medical records and telephone interviews. All patients included in the present study underwent RECIST 1.1 assessment by chest CT imaging within 7 days prior to the initiation of TRT, to ensure the homogeneity of the study cohort and to ensure that all patients received appropriate treatment.

**RT protocols.** All patients received intensity-modulated conformal RT. The tumor target volumes and doses were defined as the primary thoracic lesion and metastatic mediastinal lymph nodes. Extrathoracic metastatic sites were not included. Palliative RT for thoracic lesions was delivered at a total dose of 50-60 Gy in 25-30 fractions, with a single fraction dose of 1.8-2.0 Gy. Organ-at-risk (OAR) dose constraints were as follows: i) Spinal cord, maximum dose <45 Gy; ii) ipsilateral lung, volume of the OAR receiving at least 5 Gy (V5)  $\leq 65\%$ , V20  $\leq 30\%$ , and V30  $\leq 20\%$ ; iii) bilateral lungs, V20  $\leq 28\%$ ; iv) heart, V30  $\leq 30\%$  and mean dose <35 Gy; v) esophagus, V50  $\leq 50\%$  and mean dose <34 Gy; vi) liver, V30 <30%; vii) kidney, V20 <30%; and viii) trachea, maximum dose <60 Gy. All patient target volumes were delineated by the same RT team.

The follow-up period for each patient began on the first day of osimertinib administration and concluded on December 31, 2023, or the date of mortality. No further radiological data on target lesions were collected after disease progression. The status of initial lesions, treatment response, and disease progression for all evaluation scans were assessed by an experienced radiologist according to RECIST v1.1 criteria.

**Study endpoints.** The primary study endpoints were PFS, local PFS (LPFS), and OS. PFS was defined as the time from the first day of targeted therapy administration until the date of radiologically confirmed disease progression or the date of last follow-up. LPFS was defined as the time from the first day of targeted therapy until radiologically confirmed progression of the intrathoracic lesion or the date of last follow-up. OS was defined as the time from the first day of targeted therapy until mortality from any cause or the date of last follow-up.

The treatment interval was defined as the number of days between the date of the first osimertinib administration and the date of the first fraction of chest RT. Oligometastasis was defined as having a total of <5 metastatic lesions in  $\leq 3$  affected organs, excluding the primary intrapulmonary lesion. Extensive metastasis was defined as having a total of >6 metastatic lesions and/or >4 affected organs. Radiation-related toxicities included radiation pneumonitis and radiation esophagitis.

**Statistical analysis.** Clinical and follow-up data of the patients were retrospectively extracted from the hospital's electronic medical record system between January 2025 and March 2025, and all retrospective statistical analyses were completed within this timeframe. The primary outcome

examined was the relationship between RT intervals and prognosis. Demographic and pathological factors were evaluated as potential influencing factors. Data that followed a normal distribution are presented as mean  $\pm$  standard deviation, whilst skewed data are expressed as median [interquartile range (IQR)]. Categorical data are described using counts and percentages. Incomplete data were excluded to ensure that only complete data were used for further analysis. Univariate and multivariate Cox proportional hazards regression models were used to identify potential influencing factors that may affect prognosis. Baseline characteristics were compared between groups using the  $\chi^2$  test for categorical variables and the Mann-Whitney U test for continuous variables. The association between RT intervals and the prognosis was described using univariate and multivariable Cox regression with the visual 4-knots restricted cubic splines (RCS) model. Variables with  $P < 0.1$  in univariate Cox analyses were adjusted in the multivariate model, which is consistent with standard epidemiological practice. This approach avoids over-restrictive  $P < 0.05$  thresholds that can introduce model bias by excluding important prognostic variables, and adheres to the 10 events per variable rule. If non-linearity was detected, the inflection point was first calculated using a recursive algorithm, before a three-piecewise Cox proportional-hazards regression model was then constructed on both sides of the inflection point. The cumulative rates of mortality were compared using the Kaplan-Meier curves. For sensitivity analysis, intervals were categorized into tertiles and quartiles using a recursive algorithm before the associations between the quartiles of intervals and prognosis were calculated. Stratified analysis was performed by mutation type. The response to osimertinib was considered as a covariate in the additional multivariate analyses for confounding factor adjustment. To address immortal time bias, left-truncated time-dependent Cox regression and RCS models were used. In these models, patients entered the risk set only from TRT initiation rather than from osimertinib commencement. Landmark analyses at 3, 6, and 12 months were further conducted by excluding patients with short follow-up before each landmark cut-off. Multivariable Cox models and Kaplan-Meier curves were repeated, with log-rank tests applied to compare inter-group survival differences. Landmark Kaplan-Meier curves stratified according to the median treatment interval were plotted to compare survival outcomes across the two subgroups. Splitting at the median treatment interval in Landmark Kaplan-Meier curves was performed to compare markedly distinct survival. To balance baseline characteristics, inverse probability of treatment weighting (IPTW), which is based on the generalized propensity score, was performed to balance baseline characteristics across different interval groups. Pearson's correlation was used to evaluate covariate balance, with a Pearson's correlation coefficient  $< 0.1$  defined as adequate balance. Weighted Cox regression was conducted with the multivariable-adjusted primary model.

All statistical analyses were conducted in R 4.3.1 utilizing four CRAN-hosted packages: Survival (<https://cran.r-project.org/web/packages/survival>), rms (<https://cran.r-project.org/web/packages/rms>), dplyr (<https://cran.r-project.org/web/packages/dplyr>) and survminer (<https://cran.r-project.org/web/packages/survminer>).

Two-sided  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

**Patient characteristics.** A total of 179 patients with advanced NSCLC initially received first-line osimertinib at The Fourth Affiliated Hospital of Guangxi Medical University. From this cohort, 175 met the inclusion criteria. Due to the use of RT before drug treatment, 4 patients were excluded from the cohort study (Fig. S1). Amongst the remaining patients, there were no cases of missing data. The cohort included 110 males and 65 females. According to tumor, node, and metastasis (TNM) classification distribution (16), there were 29 patients with stage IIIB and 146 with stage IV disease. The median age was 61 years [95% confidence interval (CI), 29-88]. A total of 55 patients (31.4%) were older than 65 years, and 39 (22.3%) had a history of smoking. Among the cohort, 40 patients had oligometastasis, whilst 135 had extensive metastasis. By ECOG performance status, there were 142 patients in the 0-1 points category and 33 patients in the 2 points category. In total, 96 patients had an EGFR exon 19 deletion and 79 had an EGFR exon 21 L858R point mutation. The demographic and oncological characteristics of the patients are summarized in Table I. The median treatment interval was 67 days (IQR, 72.50 days), with a mean of 71.66 days (95% CI, 64.98-78.35). The 29 patients with stage IIIB disease included in the present study showed no significant differences in baseline characteristics compared with those with stage IV disease (Table SI). The responses to osimertinib treatment before TRT were as follows: 116 cases (66.3%) with a partial response and 59 cases (33.7%) with stable disease (Table SII).

**Treatment outcomes and toxicities.** As of the final follow-up, the median follow-up time was 25.3 months (IQR, 16.50 months). Events were observed in 155 patients (88.6%) for LPFS (local progression), in 160 patients (91.4%) for PFS (disease progression) and in 118 patients (67.4%) for OS (death from any cause). The median LPFS time was 17.50 months (IQR, 10.40 months), the median PFS time was 14.40 months (IQR, 8.20 months), and the median OS time was 25.60 months (IQR, 16.75 months). During the study period, 66 patients were diagnosed with radiation pneumonitis and 33 with radiation esophagitis. For patients who developed metastases in extra-regional sites, radiation therapy was administered to the corresponding locations. When patients developed drug resistance or experienced severe adverse reactions, the treatment was switched to a second-line or subsequent-line therapy.

**Analysis.** Univariate Cox regression analysis indicated that treatment interval was a candidate prognostic factor for LPFS, PFS and OS (all in  $P < 0.001$ ), whereas age was only predictive of LPFS ( $P = 0.002$ ) and PFS ( $P < 0.001$ ) (Tables II-IV). As illustrated in Table IV, stage IV disease ( $P = 0.056$ ) and EGFR exon 21 L858R mutation ( $P = 0.045$ ) yielded significant associations with OS. Multivariate regression analysis revealed that both treatment interval [hazard ratio (HR), 1.02; 95% CI, 1.01-1.02;  $P < 0.001$ ] and age  $\geq 65$  years (HR, 0.57; 95% CI, 0.39-0.81;  $P = 0.002$ ) were significantly associated with LPFS (Table II). For PFS, multivariate regression showed that

Table I. Characteristics of the 175 patients.

| Characteristics                           | Value       |
|-------------------------------------------|-------------|
| Age, n (%)                                |             |
| <65 years                                 | 120 (68.57) |
| ≥65 years                                 | 55 (31.43)  |
| Sex, n (%)                                |             |
| Male                                      | 110 (62.86) |
| Female                                    | 65 (37.14)  |
| Smoking history, n (%)                    |             |
| No                                        | 136 (77.71) |
| Yes                                       | 39 (22.29)  |
| Family history of malignant tumors, n (%) |             |
| No                                        | 153 (87.43) |
| Yes                                       | 22 (12.57)  |
| TMN stage, n (%)                          |             |
| IIIB                                      | 29 (16.57)  |
| IV                                        | 146 (83.43) |
| Distant metastasis, n (%)                 |             |
| Oligometastasis                           | 40 (22.86)  |
| Extensive metastasis                      | 135 (77.14) |
| PS score/ECOG score, n (%)                |             |
| 0-1                                       | 142 (81.14) |
| 2                                         | 33 (18.86)  |
| Genetic typing, n (%)                     |             |
| EGFR 19 exon mutation                     | 96 (54.86)  |
| EGFR exon 21 L858R point mutation         | 79 (45.14)  |
| Treatment interval, days                  |             |
| Median                                    | 67          |
| Range                                     | 38-111      |

TNM, Tumor-Node-Metastasis; PS, performance status; ECOG, Eastern Cooperative Oncology Group.

treatment interval (HR, 1.01; 95% CI, 1.01-1.02;  $P<0.001$ ) and age  $\geq 65$  years (HR, 0.51; 95% CI, 0.36-0.73;  $P<0.001$ ) were significantly associated with outcome (Table III). In terms of OS, univariate Cox regression analysis showed that TNM stage, EGFR mutation subtype, and treatment interval were potential influencing factors. Multivariate regression analysis further demonstrated that EGFR mutation subtype (HR, 1.47; 95% CI, 1.01-2.13;  $P=0.045$ ) and treatment interval (HR, 1.02; 95% CI, 1.01-1.02;  $P<0.001$ ) were significantly associated with OS (Table IV). In the sensitivity analysis, the risk estimates of the treatment interval for prognosis remained significantly associated with LPFS, PFS and OS across the tertile groups (Tables SIII-SV).

After controlling for covariates, longer treatment intervals remained non-linearly correlated with survival endpoints, with significant non-linear relationships observed for LPFS (non-linear  $P=0.003$ ), PFS (non-linear  $P=0.010$ ) and OS (non-linear  $P=0.004$ ) (Fig. 1). Using three-piecewise linear regression models, it was determined that 40 and 102 days were the inflection points for LPFS (Fig. 2), whilst 40 and 104 days

were the inflection points for PFS and OS (Figs. 3 and 4). For LPFS, the risk rapidly increased between 40 and 102 days (HR, 1.03; 95% CI, 1.02-1.04;  $P<0.001$ ). A highly similar pattern was observed for PFS (HR, 1.03; 95% CI, 1.02-1.04;  $P<0.001$ ) and OS (HR, 1.04; 95% CI, 1.02-1.05;  $P<0.001$ ). When outside of the threshold (such as before 40 days or after the upper threshold), the prognostic risk of LPFS, PFS, and OS did not change significantly.

Patients were then divided into three groups. In the Kaplan-Meier curve, longer LPFS, PFS, and OS times were observed in patients in the early-treatment group ( $<40$  days; log-rank test,  $P<0.001$ ; Fig. 5). In the sensitivity analysis, after adjusting for the response to osimertinib, the treatment interval remained an independent prognostic factor for LPFS (HR, 1.02; 95% CI, 1.01-1.02;  $P<0.001$ ), PFS (HR, 1.01; 95% CI, 1.01-1.02;  $P<0.001$ ), and OS (HR, 1.02; 95% CI, 1.01-1.02;  $P<0.001$ ) (Tables SVI-VIII). Furthermore, after adjustment, the original non-linear association remained statistically significant (Fig. S2). In left-truncated time-dependent Cox regression, a longer RT interval remained significantly associated with worse LPFS and PFS, whereas no meaningful association with OS was detected (Table SIX). Left-truncated RCS models showed significant non-linear relationships between the RT interval and OS, PFS, and LPFS (Fig. S3). In landmark analyses at 3, 6, and 12 months, for each 1-day increase in the interval, the rate of adverse survival risks increased significantly for OS, PFS, and LPFS across all landmark time points (Fig. S4). Kaplan-Meier curves in the landmark analysis stratified by the median 67-day treatment interval revealed significant differences in LPFS, PFS and OS between subgroups (all  $P<0.0001$ ). Patients with treatment intervals  $<67$  days achieved longer survival than those with intervals of  $\geq 67$  days (Figs. S5-7). In the four-piecewise Cox regression model, when the treatment interval exceeded the threshold of 67 days, longer intervals were closely associated with poor prognosis for LPFS, PFS, and OS (Fig. S8; Tables SX-XII). Subgroup analysis showed that prolonged RT interval independently predicted poorer prognosis across both EGFR subtypes (Table SXIII). After adjustment for confounding covariates, a significant interaction was identified between EGFR genotype and treatment interval with respect to OS. No comparable significant interaction was found for PFS or LPFS (Table SXIII). After IPTW, all baseline covariates were well-balanced (Table SXIV). IPTW-weighted Cox regression confirmed that prolonged RT interval remained significantly associated with inferior OS, PFS, and LPFS (Table SXV). IPTW-RCS showed significant non-linear trends (Fig. S9).

## Discussion

To the best of our knowledge, the relationship between the treatment interval for chest RT and prognosis in patients with advanced NSCLC treated with first-line osimertinib has not been sufficiently analyzed. A key novel finding of the present study is the significant impact of RT interval on prognosis and their non-linear relationship. Treatment interval was significantly associated with LPFS, PFS, and OS. In the middle intervals (40-102 days/40-104 days), the risk rapidly

Table II. Univariate and multivariate cox regression for predictors of local progression-free survival.

| Characteristic                     | Univariable |           |         | Multivariable |           |         |
|------------------------------------|-------------|-----------|---------|---------------|-----------|---------|
|                                    | HR          | 95% CI    | P-value | HR            | 95% CI    | P-value |
| Age ≥65 years                      | 0.61        | 0.43-0.88 | 0.007   | 0.57          | 0.39-0.81 | 0.002   |
| Female                             | 1.04        | 0.75-1.44 | 0.82    |               |           |         |
| Smoking history                    | 1.06        | 0.73-1.53 | 0.779   |               |           |         |
| Family history of malignant tumors | 0.80        | 0.48-1.33 | 0.388   |               |           |         |
| TMN stage IV                       | 0.98        | 0.64-1.51 | 0.937   |               |           |         |
| Extensive metastasis               | 0.85        | 0.59-1.22 | 0.378   |               |           |         |
| PS score/ECOG score                | 1.01        | 0.67-1.51 | 0.977   |               |           |         |
| EGFR exon 21 L858R point mutation  | 1.02        | 0.74-1.40 | 0.910   |               |           |         |
| Treatment interval, days           | 1.02        | 1.01-1.02 | <0.001  | 1.02          | 1.01-1.02 | <0.001  |
| Radiation-induced lung injury      | 1.06        | 0.77-1.47 | 0.719   |               |           |         |
| Radiation-induced esophagitis      | 1.16        | 0.78-1.74 | 0.465   |               |           |         |

CI, confidence interval; HR, hazard ratio; TNM, Tumor-Node-Metastasis; PS, performance status; ECOG, Eastern Cooperative Oncology Group.

Table III. Univariate and multivariate cox regression for predictors of progression-free survival.

| Characteristic                     | Univariable |           |         | Multivariable |           |         |
|------------------------------------|-------------|-----------|---------|---------------|-----------|---------|
|                                    | HR          | 95% CI    | P-value | HR            | 95% CI    | P-value |
| Age ≥65 years                      | 0.55        | 0.38-0.78 | <0.001  | 0.51          | 0.36-0.73 | <0.001  |
| Female                             | 1.04        | 0.75-1.43 | 0.821   |               |           |         |
| Smoking history                    | 1.02        | 0.71-1.48 | 0.903   |               |           |         |
| Family history of malignant tumors | 0.71        | 0.43-1.18 | 0.188   |               |           |         |
| TMN stage IV                       | 1.06        | 0.69-1.63 | 0.782   |               |           |         |
| Extensive metastasis               | 0.77        | 0.54-1.11 | 0.157   |               |           |         |
| PS score/ECOG score                | 1.02        | 0.68-1.53 | 0.910   |               |           |         |
| EGFR exon 21 L858R point mutation  | 0.98        | 0.71-1.34 | 0.887   |               |           |         |
| Treatment interval, days           | 1.01        | 1.01-1.02 | <0.001  | 1.01          | 1.01-1.02 | <0.001  |
| Radiation-induced lung injury      | 1.10        | 0.80-1.52 | 0.558   |               |           |         |
| Radiation-induced esophagitis      | 1.16        | 0.78-1.74 | 0.46    |               |           |         |

CI, confidence interval; HR, hazard ratio; TNM, Tumor-Node-Metastasis; PS, performance status; ECOG, Eastern Cooperative Oncology Group.

increased for LPFS, PFS, and OS. However, outside this threshold range, no significant change in prognostic risk was observed. In the Kaplan-Meier curve, patients treated early had a superior prognosis in terms of LPFS, PFS, and OS. These findings indicate that TRT initiation within 40 days of osimertinib commencement is associated with maximal survival benefit, whilst delays between 40 and 104 days confer a significantly elevated risk of disease progression and mortality.

The sensitivity of NSCLC to RT is low, and the timing of radiation therapy initiation remains a controversial issue. Previous studies have shown that the benefit of EGFR-TKI combined with RT in terms of PFS is superior compared with

that of combined anti-angiogenesis therapy, chemotherapy, and any other treatment (17), in addition to being superior to EGFR-TKI alone (18). In terms of mechanism, there is evidence that the combination of EGFR-TKI and RT can significantly reduce the proportion of S-phase cells, induce apoptosis, inhibit the autophosphorylation of epidermal EGFR and downregulate the expression of Rad51 recombinase to enhance radiosensitivity (19). Similarly, induction chemotherapy before RT has a benefit on the OS of patients with NSCLC receiving RT and chemotherapy (20), which indicates the rationality of EGFR-TKI therapy combined with consolidation RT. However, Xu *et al* (21) enrolled 45 patients with stage III NSCLC treated with concurrent radiotherapy

Table IV. Univariate and multivariate cox regression for predictors of overall survival.

| Characteristic                     | Univariable |           |         | Multivariable |           |         |
|------------------------------------|-------------|-----------|---------|---------------|-----------|---------|
|                                    | HR          | 95% CI    | P-value | HR            | 95% CI    | P-value |
| Age $\geq 65$ years                | 1.10        | 0.74-1.62 | 0.641   |               |           |         |
| Female                             | 1.01        | 0.69-1.46 | 0.975   |               |           |         |
| Smoking history                    | 0.83        | 0.52-1.30 | 0.411   |               |           |         |
| Family history of malignant tumors | 1.01        | 0.59-1.75 | 0.965   |               |           |         |
| TNM stage IV                       | 2.07        | 1.14-3.77 | 0.017   | 1.79          | 0.98-3.27 | 0.056   |
| Extensive metastasis               | 1.05        | 0.68-1.62 | 0.842   |               |           |         |
| PS score/ECOG score                | 1.03        | 0.64-1.63 | 0.914   |               |           |         |
| EGFR exon 21 L858R point mutation  | 1.68        | 1.16-2.43 | 0.006   | 1.47          | 1.01-2.13 | 0.045   |
| Treatment intervals, days          | 1.02        | 1.01-1.02 | <0.001  | 1.02          | 1.01-1.02 | <0.001  |
| Radiation-induced lung injury      | 1.22        | 0.84-1.77 | 0.301   |               |           |         |
| Radiation-induced esophagitis      | 1.34        | 0.85-2.13 | 0.206   |               |           |         |

CI, confidence interval; HR, hazard ratio; TNM, Tumor-Node-Metastasis; PS, performance status; ECOG, Eastern Cooperative Oncology Group.

plus EGFR-TKIs, 20 of whom (44.4%) harbored EGFR mutations. The cohort achieved a median PFS time of 27.9 months (95% CI, 18.7-37.2) and a median OS time of 49.7 months (95% CI, 27.7-71.8). Different from this concurrent treatment strategy, the present study adopted sequential EGFR-TKI consolidation following radiotherapy and included patients with stage IV disease, who generally have poorer baseline prognostic outcomes. Despite this disadvantage at baseline, the patients still achieved promising survival outcomes, which may be explained by the longer median duration of EGFR-TKI treatment in the present cohort (28.4 vs. 14.4 months) compared with that of the cohort in the study by Xu *et al* (21). Previous studies found that the treatment time was positively associated with OS (21), which was also the reason for the shorter median OS time observed in the present cohort. Hu *et al* (22) adopted a similar treatment strategy to the present study, combining EGFR-TKIs with local consolidative radiotherapy. Nevertheless, the cohort achieved a longer median OS time than in the present study (38.0 vs. 25.6 months). This survival discrepancy was mainly attributed to differences in baseline patient characteristics, as the study only enrolled elderly patients with oligometastatic disease who carried more favorable prognostic profiles (22). Importantly, while baseline patient characteristics and EGFR-TKI treatment duration have been established as prognostic predictors for EGFR-mutant NSCLC (23), few studies have specifically investigated how the time interval between EGFR-TKI initiation and thoracic radiotherapy affects long-term survival. Although this temporal parameter has not yet been fully characterized, it bears important clinical implications for guiding the optimal sequencing of targeted therapy and radiotherapy.

The present study shows that the intervals of 40 and 102/104 days are the inflection points for the therapeutic effect of the time interval between EGFR-TKI initiation and thoracic radiotherapy. Within 40-102/104 days, the longer interval is associated with a higher probability of adverse

prognostic risk. EGFR-TKI can inhibit the proliferation and survival of tumor cells while altering the immune environment (22). When the interval between EGFR-TKI and RT is short, EGFR-TKI and RT can exert synergistic effects, making the killing effect of RT on tumor cells more potent (24,25). This can explain the time trend of the RT effect observed in the present study. An interval of <30 days may be too brief to permit full TKI-mediated radiosensitization, attenuating clinical benefit. Li *et al* (26) observed that primary tumor radiotherapy initiated 30 days after EGFR-TKI yielded better overall survival than either earlier treatment or post-progression radiotherapy, but did not evaluate non-linear interval effects. Several lines of evidence support the rationality of the upper limit of 102/104 days for radiotherapy initiation identified. Tang *et al* (27) found that patients receiving single-agent EGFR-TKIs achieved a median time to therapeutic response of 2.00 months (95% CI, 1.28 to 2.92 months). For patients with stable disease, the median time to maximum tumor shrinkage was also 2.00 months, corresponding to a 95% CI of 1.42-2.58 months. These clinical observations align with another independent study confirming that effective antitumor responses can be achieved within 8 weeks after EGFR-TKI treatment initiation (27). Therefore, these published data presented above reveal that EGFR-TKIs mostly induce maximal tumor regression within the first 2 months of treatment. This temporal characteristic matches the 67-day breakpoint observed in the present restricted cubic spline analysis. Radiotherapy delayed beyond this time point correlates with an elevated risk of local disease progression. Such temporal consistency further supports the biological rationality of the present findings. Clinically, administering thoracic radiotherapy after EGFR-TKI-induced tumor shrinkage, and before the development of drug resistance and tumor regrowth, constitutes an optimal treatment window to maximize local tumor control. This appropriate time window opens 6 to 8 weeks after TKI administration and closes no later than 102 to 104 days after TKI initiation.

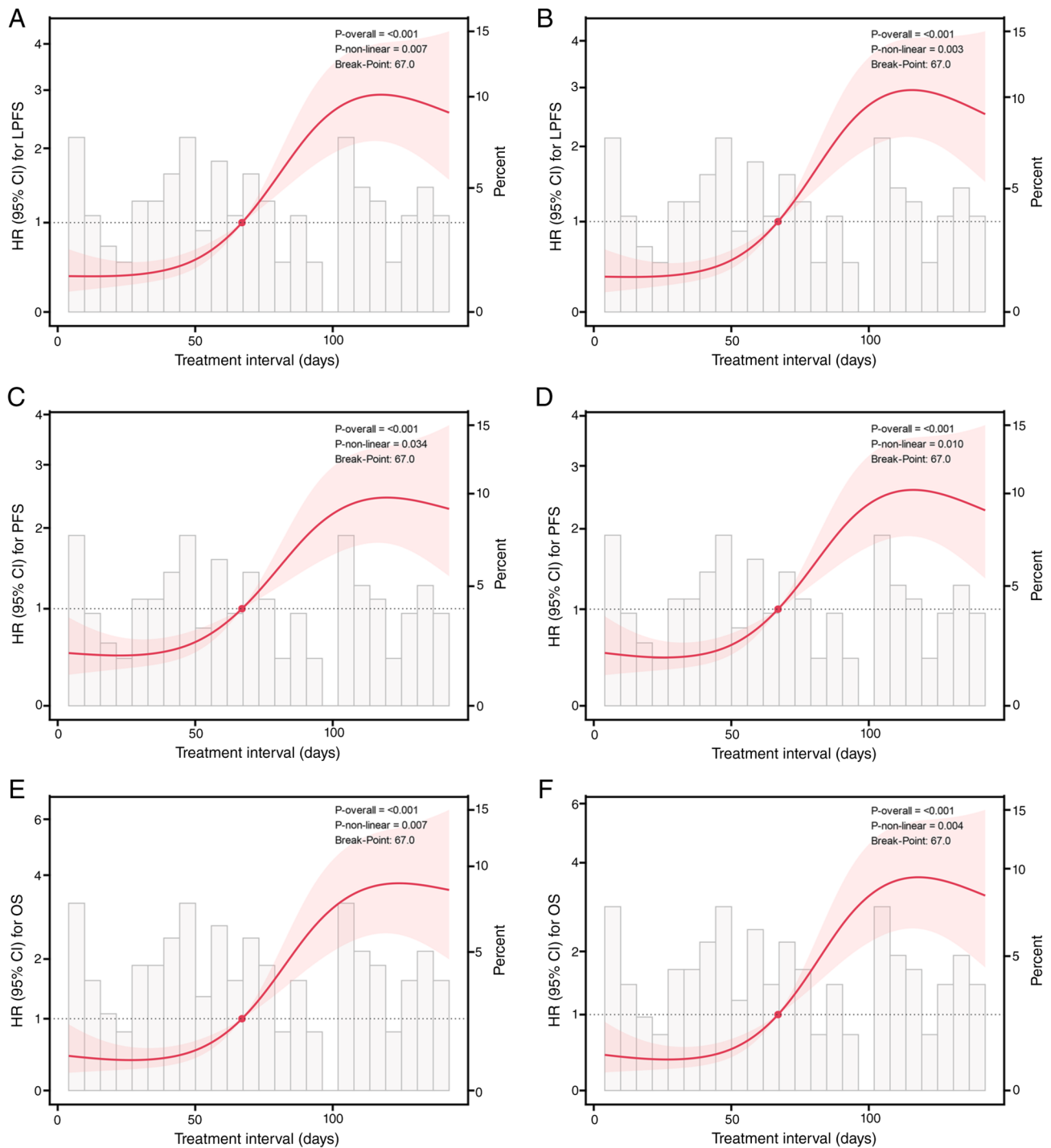


Figure 1. Restricted cubic spline curves between osimertinib-to-thoracic radiotherapy interval and risk of LPFS, PFS and OS. Solid lines represent hazard ratios, shaded areas represent 95% confidence intervals, and dashed lines indicate HR=1. (A and B) LPFS, (C and D) PFS and (E and F) OS curves. (A, C and E) Unadjusted and (B, D and F) multivariable-adjusted models [(B) and (D) are adjusted for age; (F) is adjusted for Tumor-Node-Metastasis stage and EGFR mutation subtype]. PFS, progression-free survival; LPFS, local PFS; OS, overall survival; HR, hazard ratio; CI, confidence interval.

In the present study, restricted cubic spline and piecewise regression analyses confirmed a non-linear association between the osimertinib-to-TRT interval and survival outcomes. In the present results, the mortality risk remained stable for intervals of <40 days and rose significantly for intervals between 40 and 102 days, before plateauing again for intervals >102 days. This trend may be attributed to the dynamic changes in tumor cell cycle status, immune micro-environment evolution, and clinical confounding factors.

This interval-specific elevation in risk may be primarily driven by the waning of osimertinib-induced radiosensitization. Preclinical studies in EGFR-mutant NSCLC models have demonstrated that EGFR-TKI induces G<sub>1</sub> cell cycle arrest and exerts transient radiosensitizing effects (28,29). This radiosensitization gradually diminishes with prolonged drug exposure, as surviving tumor cells restore proliferative capacity via upregulation of cyclin D1 and CDK4/6 signaling (30-32). By 40 days post-initiation, the majority of

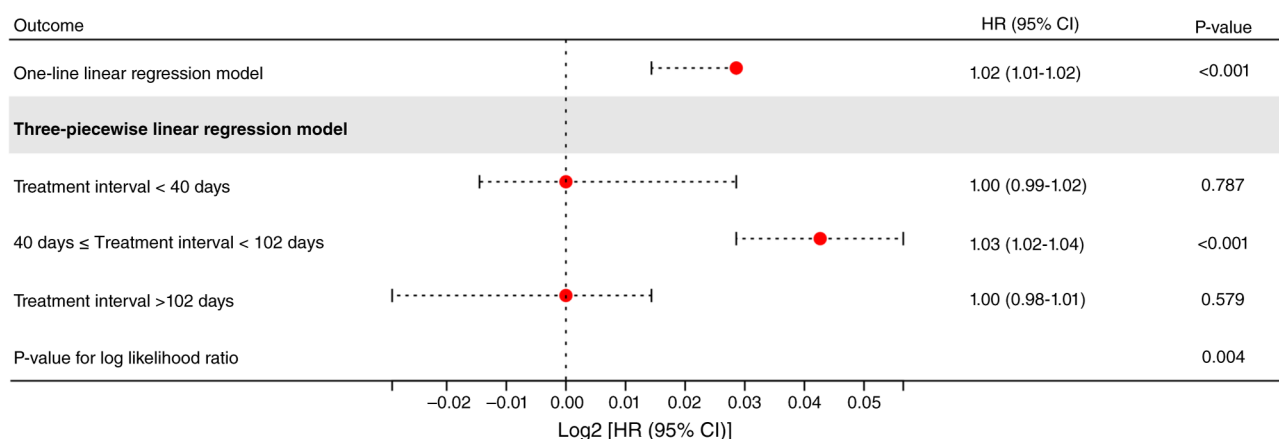


Figure 2. Inflection point analysis of treatment interval effect on local progression-free survival adjusted for age. HR, hazard ratio; CI, confidence interval.

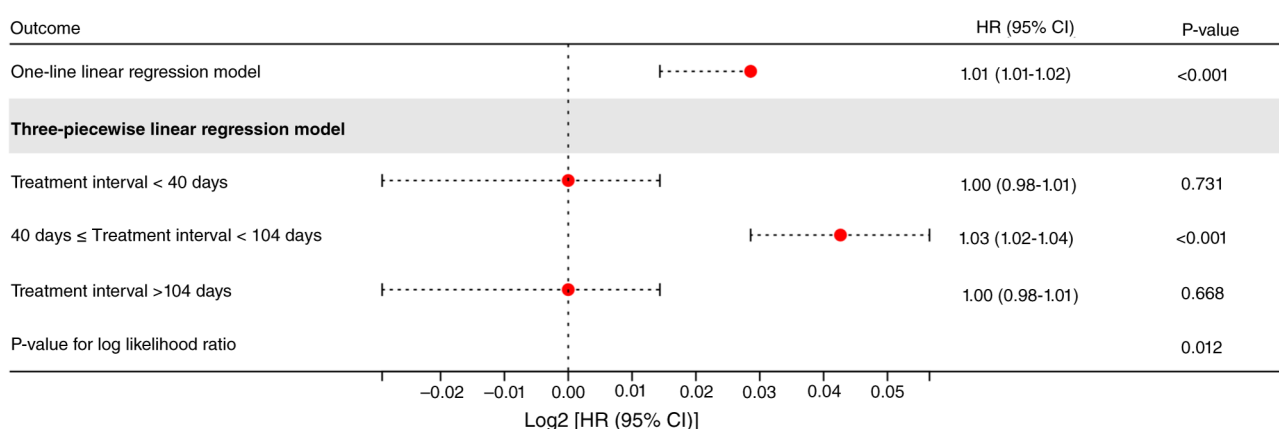


Figure 3. Inflection point analysis of treatment interval effect on progression-free survival adjusted for age. HR, hazard ratio; CI, confidence interval.

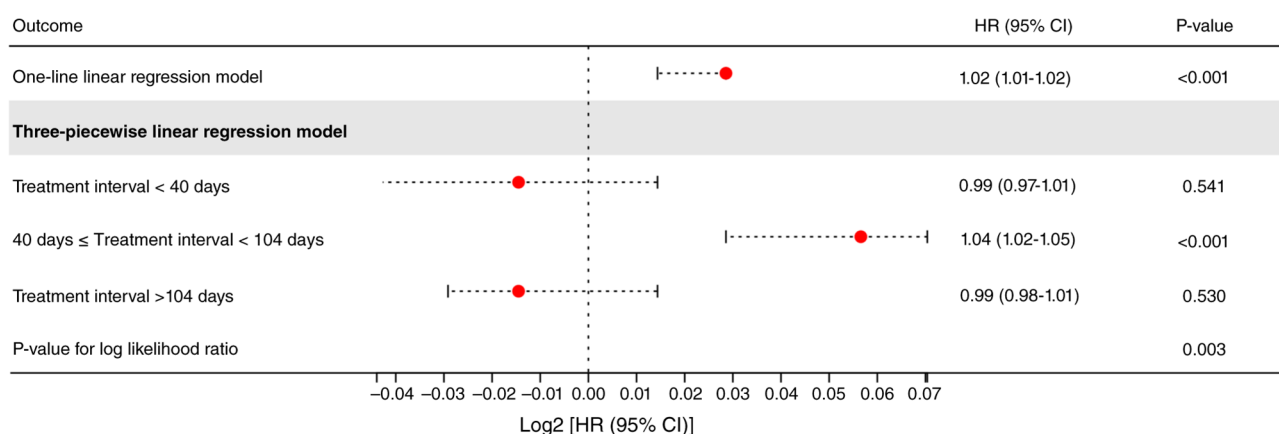


Figure 4. Inflection point analysis of treatment interval effect on overall survival adjusted for Tumor-Node-Metastasis stage and genetic typing. HR, hazard ratio; CI, confidence interval.

surviving tumor cells have exited  $G_1$  arrest. The upregulation of cyclin D1 and CDK4/6 signaling restores their proliferative capacity and reverses intrinsic radiosensitivity by a 2-times decrease compared with those in the first 2 weeks of the treatment period. Furthermore, this 40-102-day window corresponds to a transient immunosuppressive phase under continuous EGFR inhibition. In a phase III FLAURA trial, the

proportion of immunosuppressive M2-polarised tumor-associated macrophages and regulatory T cells was found to be notably increased between 6 and 14 weeks post-osimertinib initiation (33). A 2.1-times rise in tumor cell programmed death ligand 1 (PD-L1) expression is observed at 12 weeks. Consistent with a prior finding (26), long-term single-agent EGFR-TKI exposure can progressively consolidate the tumor

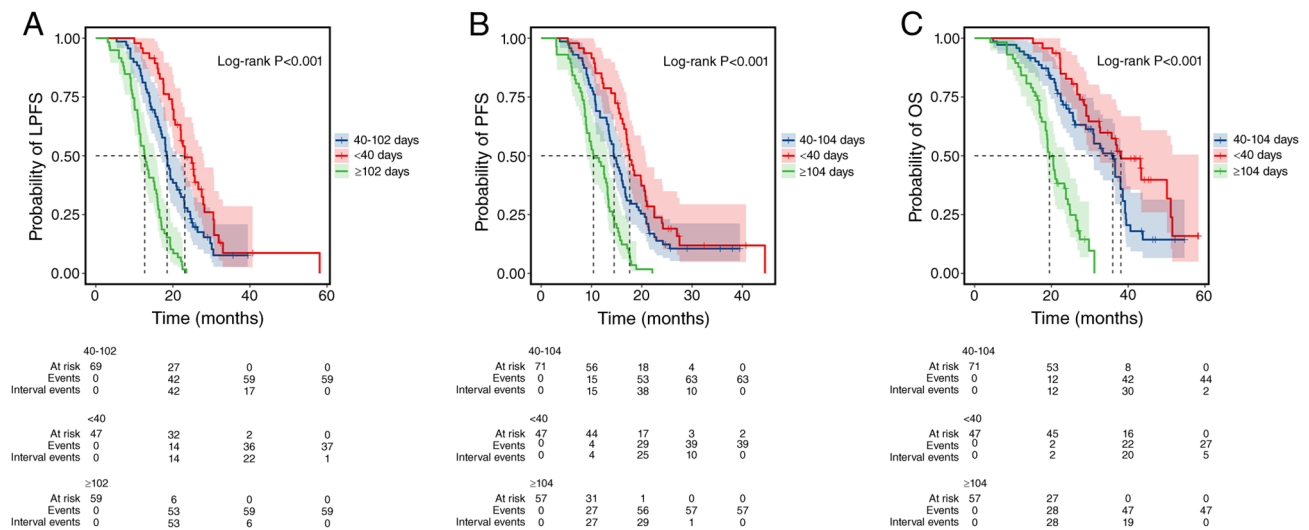


Figure 5. Survival outcomes according to treatment initiation time. (A) LPFS, (B) PFS and (C) OS curves for the early-treatment group (<40 days), middle group (40-102 days for LPFS; 40-104 days for PFS and OS) and delayed-treatment group (≥102 days for LPFS; ≥104 days for PFS and OS). Differences among the three groups were statistically significant for all endpoints (Log-rank P<0.001). LPFS, local progression-free survival; PFS, progression-free survival; OS, overall survival.

microenvironment into a deeply immunosuppressive state, promoting drug resistance and immune escape. Whilst RT can induce immunogenic cell death and promote antitumor immune responses (34,35), it also instantaneously upregulates immunosuppressive molecules, such as PD-L1, indoleamine 2,3-dioxygenase 1, and TGF- $\beta$ , while activating regulatory T cell and myeloid-derived suppressor cell function (36). Regardless of the local radiation dose, within the 40- to 102-day window, the pre-existing immunosuppressive milieu may blunt the RT-induced abscopal effect, eliminating the synergistic benefit of combined treatment. A previous retrospective cohort study demonstrated that RT initiated within this interval was associated with a 1.8-times higher risk of early local progression relative to intervals greater than or less than this threshold, with no notable difference in grade  $\geq 2$  radiation toxicity between groups (37). The observed plateau in mortality risk for intervals >102 days likely reflects clinical confounding. Patients requiring delayed RT beyond this point typically have rapidly progressive disease or severe local symptoms. In such cases, RT is delivered for palliative symptom control rather than with curative intent, leading to an inherently poor prognosis independent of timing. Although further mechanistic validation with longitudinal immune microenvironment profiling is warranted, this interval-specific risk likely reflects the convergence of lost cell cycle-mediated radiosensitivity and transient immunosuppression. Future studies establishing multi-omic prediction models for optimal EGFR-TKI-RT interval will enable real-time individualized treatment timing to improve patient outcomes.

In the present study, the EGFR exon 21 L858R point mutation was identified as an independent prognostic factor significantly associated with OS. This finding is consistent with the general understanding that patients harboring EGFR mutations exhibit enhanced sensitivity to EGFR-TKIs (37), consequently leading to prolonged OS times compared with patients harboring wild-type EGFR (38). However, within the

spectrum of common activating mutations, exon 19 deletions are generally considered to confer a superior median OS time over the L858R mutation in the setting of first-line EGFR-TKI treatment (39,40). This difference is typically mechanistically ascribed to distinct structural alterations present within the EGFR-TKI binding domain, which confer greater TKI sensitivity to the exon 19 deletion subtype (41,42).

A notable discrepancy observed in the present cohort was the lack of a significant prognostic effect of the mutation subtype on PFS, despite the strong association with OS. This difference in outcomes (PFS vs. OS) may be attributable to the established association of the L858R subtype with high-risk oncogenic features, such as a greater propensity for liver/brain metastases or concomitant *TP53* co-mutation (43,44), factors that are more robustly associated with compromised OS compared with initial PFS.

Furthermore, the mechanistic rationale for combining osimertinib with ionizing radiation (IR) is robust. *In vitro* evidence has shown that osimertinib can synergistically enhance the antitumor activity of IR by inhibiting cellular proliferation and clonal survival, reducing IR-induced G<sub>2</sub>/M cell cycle arrest and delaying DNA damage repair in a concentration- and time-dependent manner. This synergy is also mediated by effectively blocking the phosphorylation of EGFR (Tyr1068/Tyr1173) and key downstream signaling pathways, including AKT and ERK (45). The present study established a critical time threshold for the TKI-TRT interval in the overall cohort. The observed differential impact of the L858R subtype on OS highlights the need for tailored strategies. Future large-scale, prospective investigations are therefore warranted to explore the optimal TRT initiation timing specific to individual EGFR mutation subtypes, ensuring maximized long-term clinical benefit.

The present study has several limitations. The retrospective design, single-center and relatively small sample size introduce the potential for selection bias. Although the present findings strongly suggest an optimal treatment window, the definitive

establishment of the ideal combination strategy necessitates rigorous validation through larger, prospective, multi-center trials. Furthermore, despite multivariable adjustment, IPTW weighting and rigorous immortal time bias elimination, the present study remains susceptible to unmeasured confounding, among which tumor molecular heterogeneity is particularly relevant. The clonal heterogeneity of the T790M mutation and co-existing gene mutations, such as those in *TP53*, can accelerate the development of osimertinib resistance (46). As such molecular profiles may prompt clinicians to initiate TRT earlier while independently worsening prognosis, they act as unmeasured confounders that could create a spurious association of ‘benefits of early TRT’. Another potential source of unmeasured confounding is molecular residual disease (MRD) status, typically detected through circulating tumor DNA (ctDNA) sequencing. As MRD/ctDNA data were unavailable in the present retrospective cohort, adjustments could not be made for it. However, external evidence shows that patients with undetectable MRD have a superior prognosis (47). Such patients may be preferentially assigned to delayed TRT by their physicians. This would concentrate biologically favorable cases in the delayed-TRT arm, artificially inflating its apparent survival benefit and biasing the estimated effect of TRT timing. In addition, differences in treatment regimens that patients receive subsequently can directly affect survival, which can in turn inversely influence clinician decisions regarding the timing of TRT (48).

In summary, the interval between osimertinib initiation and TRT was an independent prognostic factor with a non-linear association with clinical outcomes. TRT delivered within 40 days was associated with optimal LPFS, PFS and OS. Between 40 and 104 days, longer intervals correlated with progressively worse outcomes. Beyond 104 days, further delay did not significantly alter prognostic risk. These findings support the integration of TRT within 40 days of osimertinib initiation.

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### Availability of data and materials

The data generated in the present study are not publicly available due to privacy and ethical restrictions, but may be requested from the corresponding author.

### Authors' contribution

ML and YZ were responsible for the study analysis, developing the methodology, writing the original draft, visualization, and revision of the manuscript. ZC and XY contributed to methodology, data curation, acquisition of

clinical data, and reviewing and editing of the manuscript. WY and JH contributed to validation, data verification, endpoint adjudication, and reviewing and editing of the manuscript. DH and LQ contributed to conceptualization, supervision, project administration, resources, data interpretation, and critically revising the manuscript for important intellectual content. ML and YZ confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

The study protocol was approved by the Institutional Ethics Committee of The Fourth Affiliated Hospital of Guangxi Medical University (approval no. KY2024162). Due to the retrospective observational nature of the study and the use of fully de-identified patient data, the requirement for written informed consent was formally waived by the Institutional Ethics Committee.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

### References

1. Jia B, Zheng Q, Wang J, Sun H, Zhao J, Wu M, An T, Wang Y, Zhuo M, Li J, *et al*: A nomogram model to predict death rate among non-small cell lung cancer (NSCLC) patients with surgery in surveillance, epidemiology, and end results (SEER) database. *BMC Cancer* 20: 666, 2020.
2. Snider M, Salama JK and Boyer M: Survival and recurrence rates following SBRT or surgery in medically operable stage I NSCLC. *Lung Cancer* 197: 107962, 2024.
3. Wu YL, Planchard D, Lu S, Sun H, Yamamoto N, Kim DW, Tan DSW, Yang JC, Azrif M, Mitsudomi T, *et al*: Pan-Asian adapted clinical practice guidelines for the management of patients with metastatic non-small-cell lung cancer: A CSCO-ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS. *Ann Oncol* 30: 171-210, 2019.
4. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskuliyong B, Lee KH, Dechaphunkul A, Imamura F, Nogami N, Kurata T, *et al*: Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* 378: 113-125, 2018.
5. Nagasaka M, Zhu VW, Lim SM, Greco M, Wu F and Ou SI: Beyond osimertinib: The development of third-generation EGFR tyrosine kinase inhibitors for advanced EGFR+ NSCLC. *J Thorac Oncol* 16: 740-763, 2021.
6. Cho JH, Lim SH, An HJ, Kim KH, Park KU, Kang EJ, Choi YH, Ahn MS, Lee MH, Sun JM, *et al*: Osimertinib combined with gefitinib in patients with EGFR-mutated non-small-cell lung cancer: Open-label, phase II trial (KCSG-LU15-09). *J Clin Oncol* 38: 488-495, 2020.
7. Gomez DR, Blumenschein GR Jr, Lee JJ, Hernandez M, Ye R, Camidge DR, Doebele RC, Skoulidis F, Gaspar LE, Gibbons DL, *et al*: Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: A multicentre, randomised, controlled, phase 2 study. *Lancet Oncol* 17: 1672-1682, 2016.
8. Iyengar P, Wardak Z, Gerber DE, Tumati V, Ahn C, Hughes RS, Dowell JE, Cheedella N, Nedzi L, Westover KD, *et al*: Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: A phase 2 randomized clinical trial. *JAMA Oncol* 4: e173501, 2018.

9. Xing L, Wu G, Wang L, Li J, Wang J, Yuan Z, Chen M, Xu Y, Fu X, Zhu Z, *et al*: Erlotinib versus etoposide/cisplatin with radiation therapy in unresectable stage III epidermal growth factor receptor mutation-positive non-small cell lung cancer: A multicenter, randomized, open-label, phase 2 trial. *Int J Radiat Oncol Biol Phys* 109: 1349-1358, 2021.
10. Liu R, Wei S, Zhang Q, Zhang X, Luo H, Tian J, Li Y, Ge L and Wang X: Epidermal growth factor receptor tyrosine kinase inhibitors combined with thoracic radiotherapy or chemoradiotherapy for advanced or metastatic non-small cell lung cancer: A systematic review and meta-analysis of single-arm trials. *Medicine* 98: e16427, 2019.
11. Zhong W, Wu L, Huang L, Wang J, Shi H and Wu S: Double-dose osimertinib combined with intrathecal injection of pemetrexed improves the efficacy of EGFR-mutated non-small cell lung cancer and leptomeningeal metastasis: Case report and literature review. *Front Oncol* 14: 1377451, 2024.
12. Xu J and Wang Z: Recent advances progress of targeted drugs combined with radiotherapy for advanced non-small cell lung cancer: A review. *Front Oncol* 13: 1285593, 2023.
13. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET and Carbone PP: Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 5: 649-655, 1982.
14. Ramón-Porta R, Asamura H, Travis WD and Rusch VW: Lung cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin* 67: 138-155, 2017.
15. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, *et al*: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 45: 228-247, 2009.
16. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, Nicholson AG, Groome P, Mitchell A, Bolejack V, *et al*: The IASLC lung cancer staging project: Proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol* 11: 39-51, 2016.
17. Xue J, Li B, Wang Y, Huang Z, Liu X, Guo C, Zheng Z, Liang N, Le X and Li S: Efficacy and safety of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor combination therapy as first-line treatment for patients with advanced EGFR-mutated, non-small cell lung cancer: A systematic review and Bayesian network meta-analysis. *Cancers (Basel)* 14: 4894, 2022.
18. Zhou Y, Peng L, Liang F, Chu L, Chu X, Yang X, Zhang J, Guo T, Jiang S, Pang Y, *et al*: Safety and efficacy of consolidative stereotactic radiotherapy for oligo-residual EGFR-mutant non-small cell lung cancer after first-line third-generation EGFR-tyrosine kinase inhibitors: A single-arm, phase 2 trial. *EClinicalMedicine* 76: 102853, 2024.
19. Tsai YC, Ho PY, Tzen KY, Tuan TF, Liu WL, Cheng AL, Pu YS and Cheng JC: Synergistic blockade of EGFR and HER2 by new-generation EGFR tyrosine kinase inhibitor enhances radiation effect in bladder cancer cells. *Mol Cancer Ther* 14: 810-820, 2015.
20. Luo H, Yu X, Liang N, Xie J, Deng G, Liu Q, Zhang J, Zhang J and Ge H: The effect of induction chemotherapy in patients with locally advanced non-small cell lung cancer who received chemoradiotherapy: A systematic review and meta-analysis. *Medicine* 96: e6165, 2017.
21. Xu K, Liang J, Zhang T, Zhou Z, Chen D, Feng Q, Xiao Z, Hui Z, Lu J, Wang X, *et al*: Clinical outcomes and radiation pneumonitis after concurrent EGFR-tyrosine kinase inhibitors and radiotherapy for unresectable stage III non-small cell lung cancer. *Thorac Cancer* 12: 814-823, 2021.
22. Hu X, Li H, Kang X, Wang X, Pang H, Liu C, Zhang J and Wang Y: First-line tyrosine kinase inhibitors combined with local consolidative radiation therapy for elderly patients with oligometastatic non-small cell lung cancer harboring EGFR activating mutations. *Front Oncol* 12: 766066, 2022.
23. Liu JF, Sun XS, Yin JH and Xu XE: Adjuvant EGFR-TKI therapy in resected EGFR-mutation positive non-small cell lung cancer: A real-world study. *Front Oncol* 13: 1132854, 2023.
24. Georgakopoulos I, Kouloulas V, Ntoumas G, Desse D, Koukourakis I, Kouglioumtzopoulou A, Chapidou A, Syrgos KN and Zygianni A: Combined use of radiotherapy and tyrosine kinase inhibitors in the management of metastatic non-small cell lung cancer: A literature review. *Crit Rev Oncol Hematol* 204: 104520, 2024.
25. Zhao X, Zhang S, Sun X, Lin Y, Capone L, Ko EC, Kann BH, Li Y and Wang X: Narrative review of stereotactic body radiation therapy combined with tyrosine kinase inhibitors for oligometastatic EGFR-mutated non-small cell lung cancer: Present and future developments. *Transl Lung Cancer Res* 13: 1383-1395, 2024.
26. Li Q, Liang N, Ouyang W, Su S, Ma Z, Geng Y, Hu Y, Li H and Lu B: Appropriate delay of primary tumour radiotherapy may lead to better long-term overall survival for non-small cell lung cancer treated with EGFR-TKIs. *BMC Cancer* 24: 1053, 2024.
27. Tang Y, Xia B, Xie R, Xu X, Zhang M, Wu K, Wang B and Ma S: Timing in combination with radiotherapy and patterns of disease progression in non-small cell lung cancer treated with EGFR-TKI. *Lung Cancer* 140: 65-70, 2020.
28. Wu TH, Hsiue EH, Lee J H, Lin CC, Liao WY, Ho CC, Shih JY, Yu CJ and Yang JC: Best response according to RECIST during first-line EGFR-TKI treatment predicts survival in EGFR mutation-positive non-small-cell lung cancer patients. *Clin Lung Cancer* 19: e361-e372, 2018.
29. Wang N, Wang L, Meng X, Wang J, Zhu L, Liu C, Li S, Zheng L, Yang Z, Xing L and Yu J: Osimertinib (AZD9291) increases radio-sensitivity in EGFR T790M non-small cell lung cancer. *Oncol Rep* 41: 77-86, 2019.
30. Kriegs M, Gurtner K, Can Y, Brammer I, Rieckmann T, Oertel R, Wysocki M, Dorniock F, Gal A, Grob TJ, *et al*: Radiosensitization of NSCLC cells by EGFR inhibition is the result of an enhanced p53-dependent G1 arrest. *Radiother Oncol* 115: 120-127, 2015.
31. Starrett JH, Guernet AA, Cuomo ME, Poels KE, van Alderwerelt van Rosenburgh IK, Nagelberg A, Farnsworth D, Price KS, Khan H, Ashtekar KD, *et al*: Drug sensitivity and allele specificity of first-line osimertinib resistance EGFR mutations. *Cancer Res* 80: 2017-2028, 2020.
32. Ahsan A, Hiniker SM, Davis MA, Lawrence TS and Nyati MK: Role of cell cycle in epidermal growth factor receptor inhibitor-mediated radiosensitization. *Cancer Res* 69: 5108-5114, 2009.
33. Hara N, Ichihara E, Kano H, Ando C, Morita A, Nishi T, Okawa S, Nakasuka T, Hirabae A, Abe M, *et al*: CDK4/6 signaling attenuates the effect of epidermal growth factor receptor tyrosine kinase inhibitors in EGFR-mutant non-small cell lung cancer. *Transl Lung Cancer Res* 9: 2132-2145, 2020.
34. Chmielecki J, Gray JE, Cheng Y, Ohe Y, Imamura F, Cho BC, Lin MC, Majem M, Shah R, Rukazenkoy Y, *et al*: Candidate mechanisms of acquired resistance to first-line osimertinib in EGFR-mutated advanced non-small cell lung cancer. *Nat Commun* 14: 321, 2023.
35. Galluzzi L, Vitale I, Warren S, Adjemian S, Agostinis P, Martinez AB, Chan TA, Coukos G, Demaria S, Deutsch E, *et al*: Consensus guidelines for the definition and detection of immunogenic cell death. *J Immunother Cancer* 8: e000337, 2020.
36. Fucikova J, Kepp O, Kasikova L, Petroni G, Yamazaki T, Liu P, Zhao L, Spisek R, Kroemer G and Galluzzi L: Mechanisms and detection of immunogenic cell death in cancer therapy. *Cell Death Dis* 11: 1013, 2020.
37. Weichselbaum RR, Liang H, Deng L and Fu YX: Radiotherapy and immunotherapy: A beneficial liaison? *Nat Rev Clin Oncol* 14: 365-379, 2017.
38. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, *et al*: Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 362: 2380-2388, 2010.
39. De B, Farooqi AS, Mitchell KG, Ludmir EB, Lewis J, Rinsurongkawong W, Rinsurongkawong V, Lee JJ, Swisher SG, Gibbons DL, *et al*: Benchmarking outcomes for molecularly characterized synchronous oligometastatic non-small-cell lung cancer reveals EGFR mutations to be associated with longer overall survival. *JCO Precis Oncol* 7: e2200540, 2023.
40. Choi YJ, Lee DH, Choi CM, Lee JS, Lee SJ, Ahn JH and Kim SW: Randomized phase II study of paclitaxel/carboplatin intercalated with gefitinib compared to paclitaxel/carboplatin alone for chemotherapy-naïve non-small cell lung cancer in a clinically selected population excluding patients with non-smoking adenocarcinoma or mutated EGFR. *BMC Cancer* 15: 763, 2015.
41. Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, Yamamoto N, Zhou C, Hu CP, O'Byrne K, Feng J, *et al*: Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): Analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol* 16: 141-151, 2015.

42. Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, Zhou C, Reungwetwattana T, Cheng Y, Chewaskulyong B, *et al*: Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med* 382: 41-50, 2020.
43. Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, Kris MG, Miller VA, Ladanyi M and Riely GJ: Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res* 19: 2240-2247, 2013.
44. Le X, Molife C, Leusch MS, Rizzo MT, Peterson PM, Caria N, Chen Y, Gugel EG and Visseren-Grul C: TP53 co-mutation status association with clinical outcomes in patients with EGFR-mutated non-small cell lung cancer. *Cancers* 14: 6127, 2022.
45. Vokes NI, Galan Cobo A, Fernandez-Chas M, Molkentine D, Treviño S III, Druker V, Qian Y, Patel S, Schmidt S, Hong L, *et al*: ATM mutations associate with distinct co-mutational patterns and therapeutic vulnerabilities in NSCLC. *Clin Cancer Res* 29: 4958-4972, 2023.
46. Vokes NI, Chambers ES, Nguyen T, Coolidge A, Lydon CA, Le X, Sholl L, Heymach JV, Nishino M, Van Allen EM and Jänne PA: Concurrent TP53 mutations facilitate resistance evolution in EGFR-mutant lung adenocarcinoma. *J Thorac Oncol* 17: 779-792, 2022.
47. Qiu B, Guo W, Zhang F, Lv F, Ji Y, Peng Y, Chen X, Bao H, Xu Y, Shao Y, *et al*: Dynamic recurrence risk and adjuvant chemotherapy benefit prediction by ctDNA in resected NSCLC. *Nat Commun* 12: 6770, 2021.
48. Shahi J, Wright JR, Gabos Z and Swaminath A: Management of small-cell lung cancer with radiotherapy-a pan-Canadian survey of radiation oncologists. *Curr Oncol* 23: 184-195, 2016.



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