The efficacy and toxicity of TRT on metastatic NSCLC in patients treated with targeted therapy and chemoimmunotherapy

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Abstract

Purpose: The role of thoracic radiotherapy (TRT)combined with first-line systemic therapy for metastatic non-small cell lung cancer (NSCLC) remains controversial. Its application is not routinely recommended due to inconsistent efficacy and toxicity risks. This study aims to identify specific patients most likely to benefit from TRT in advanced NSCLC.

Methods: A cohort included 523 patients with metastatic NSCLC from 2019-2024. Kaplan-Meier curves and log-rank tests were used to analyze progression-free survival (PFS) and overall survival (OS). Risk factors were identified using univariate and multivariate Cox regression analysis.

Results: The entire cohort median OS was 60 months and median PFS was 22 months. TRT improved both PFS (25 vs. 13 months, P<0.001) and OS (Not Reached [NR] vs. 46 months, P<0.001). In the targeted therapy group, TRT improved PFS (27 vs. 13 months, P<0.001) and OS (NR vs. 47 months, P<0.001). In the chemoimmunotherapy group, TRT improved OS (NR vs. 41 months, P=0.042) but not PFS (18 vs. 14 months, P = 0.115). Exploratory analysis found TRT increased hematologic toxicity (e.g., ≥ grade 2 lymphopenia: 67.18% vs. 11.33%, P < 0.001) and pneumonitis (any grade: 71.31% vs. 17.68%; ≥ grade 2: 17.83% vs. 4.88%, both P < 0.001). Multivariate analysis identified Planning target volume (PTV) as an independent negative predictor for PFS in the TRT group (P=0.003).

Conclusion: Adding TRT to first-line systemic therapy improves survival in metastatic NSCLC. Treatment strategies should be personalized based on molecular subtype and toxicity risk.

1.Introduction

Non-small cell lung cancer (NSCLC) accounts for 80–85% of all lung cancer cases. It is the most common malignant tumor in China. Approximately 68% of NSCLC patients in China are diagnosed at an advanced stage (stage III/IV), with stage IV accounting for the highest proportion(1). With advances in targeted therapy and immunotherapy, the treatment of NSCLC has now entered the era of molecular therapy(2–4). Patients who are positive for driver genes (such as EGFR, ALK, etc.) can benefit from targeted therapy, while patients who are negative for driver genes can also use immunotherapy. Both significantly prolonged the survival of NSCLC patients(5–10).

Although immunotherapy and targeted therapy have significantly prolonged survival outcomes, many patients still experience disease progression. For immunotherapy, the PACIFIC study showed that the median progression-free survival (PFS) was 16.8 months (95% confidence interval [CI], 13.0 to 18.1) with durvalumab(11). While the Keynote-024 study showed the median PFS was 10.3 months (95% CI, 6.7 to not reached) in the pembrolizumab group(12). In addition, the FLAURA study showed that the median PFS was 18.9 months for osimertinib (95% CI, 0.37 to 0.57; P < 0.001)(13). Radiotherapy is one of the effective treatment therapies for solid tumors and is widely used in cancer treatment(14). Previous study had shown that the use of thoracic radiotherapy (TRT) during chemoimmunotherapy or targeted therapy, or after local advance, can prolong patients' PFS and overall survival (OS) (15, 16).

Therefore, we often combine radiotherapy during first-line systemic therapy or when local progression occurs. However, some studies have shown that not all patients can get the prolonged PFS after the addition of radiotherapy. Furthermore, the addition of radiotherapy may increase the incidence of adverse events, thereby reducing the quality of life of patients(17). The objective of this study is to evaluate which treatment option, when combined with radiotherapy, can improve survival outcomes, and to identify factors that influence prognosis.

2. Methods

2.1 Patients

This retrospective study included patients with pathologically confirmed metastatic NSCLC who received first-line systemic therapy in Shandong Cancer Hospital and Institute between 2019 and 2024. Patients were categorized based on the type of first-line systemic therapy received. Those with EGFR or ALK mutations who received tyrosine kinase inhibitors (TKIs) were defined as the targeted therapy group, while patients without EGFR/ALK mutations who received chemotherapy plus immunotherapy were defined as the chemoimmunotherapy group. Within each treatment group, patients were further divided into those who received TRT and those who did not. Eligible patients met the following criteria: (1) Pathologically confirmed diagnosis of metastatic NSCLC according to the 8th edition of the AJCC TNM staging system; (2) Received first-line systemic therapy; (4) Availability of complete clinical data and imaging; (5) Survival follow-up information available for outcome analysis; (6) EGFR and ALK status were determined by polymerase chain reaction (PCR) panel or next-generation sequencing (NGS). PD-L1 expression status was determined using immunohistochemistry (IHC) technology with the DAKO 22C3 PharmDx antibody. Based on PD-L1 expression levels, patients were divided into two groups: negative group (< 1%, TPS) and positive group (≥ 1%, TPS).

2.2 Treatment and follow-up

Patients received first-line systemic therapy according to their molecular status and clinical decision-making. EGFR- or ALK-mutant patients received TKIs such as gefitinib, erlotinib, osimertinib, or alectinib, while patients with EGFR/ALK wild-type tumors were treated with platinum-based chemotherapy combined with immunotherapy. TRT was delivered either concurrently with systemic therapy, during disease control phases or after local advance. TRT was defined as radiotherapy delivered to the primary lung tumor. Radiotherapy techniques included 3D conformal radiotherapy (3D-CRT), intensity-modulated radiation therapy (IMRT). Patients were followed regularly through clinical visits and imaging every 6–12 weeks. Disease progression was assessed based on RECIST v1.1 criteria. Survival status was determined from medical records or follow-up contact. After completing treatment, patients were followed up every 3 months during the first year, every 6 months in the second year, and annually thereafter. The primary endpoint was OS, defined as the time from initiation of first-line therapy to death from any cause or last follow-up; PFS, defined as the time from initiation of first-line therapy to documented progression or death.

2.3 Statistical analysis

Continuous variables were presented as the median and interquartile range. Categorical variables were compared using the chi-square test or Fisher's exact test. OS and PFS were estimated using the Kaplan–Meier method, and differences between groups were assessed with the log-rank test. Variables with a *P*-value < 0.1 in univariate analysis were included in the multivariate models. Multivariate analysis was conducted using Cox proportional hazards models to identify independent prognostic factors for OS and PFS. Hazard ratios (HRs) and 95% CI were reported. All statistical tests were two-sided, and a *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed using Prism software version 10.1.2.

3. Results

3.1 Baseline characteristics

A total of 523 patients diagnosed with stage metastatic NSCLC were retrospectively analyzed in this study (Table 1). In the targeted therapy group, 204 patients received TRT, whereas 86 did not. Similarly, in the chemoimmunotherapy group, 155 patients underwent TRT, 78 and did not. Baseline characteristics of patients stratified by TRT status are summarized in Table 1. Most variables have no statistically significant differences between patients who received TRT and those who did not, including sex, age, ECOG performance status, smoking history, pathology type, first-line systemic treatment, T stage, N stage, brain metastasis, liver metastasis and adrenal metastasis were comparable between groups (all *P* > 0.05). There are statistical differences in lung metastasis, bone metastasis, and the number of metastases（*P* < 0.05). The specific first-line treatment therapies for patients are shown in the supplementary table (Supplementary Table).

The median follow-up time was 24 months. The treatment flowchart is presented in Figure 1.

3.2 Survival outcomes

The median OS and PFS for the entire cohort were 60 and 22 months, respectively (Figure 2A). Patients who received TRT had significantly longer PFS compared to those who did not (median PFS: 25 vs. 13 months, *P* < 0.001) (Figure 2B). TRT was also associated with a statistically significant improvement in OS (median OS: Not reached [NR] vs. 46 months, *P* < 0.001) (Figure 2C).

Among the patients receiving targeted therapy, the median PFS was 27 months in the TRT group versus 13 months in the non-TRT group (*P* < 0.001), indicating a statistically significant difference (Figure 3A). Significant differences were also observed in OS (median OS: NR vs. 47 months, *P* < 0.001) (Figure 3B). While PFS did not differ significantly between the TRT and non-TRT groups in the patients treated with chemoimmunotherapy (median PFS: 18 vs. 14 months, *P* = 0.115) (Figure 3C), OS was significantly improved in the TRT group (median OS: NR vs. 41 months, *P* < 0.042) (Figure 3D). To further explore the discordance between OS and PFS outcomes, an exploratory analysis was conducted. Patients in the

chemoimmunotherapy group were stratified based on the occurrence of pneumonia. However, no statistically significant differences in survival outcomes were observed (P = 0.45) (Figure 4).

3.3 Univariate and multivariate analyses of OS and PFS

Univariate analysis showed that age (P = 0.044) and pneumonia grade ≥ 2 (P = 0.023) were significantly associated with OS in the entire cohort. Age (P = 0.025), Planning target volume (PTV) (P = 0.047), lymphocyte grade ≥ 2(P = 0.016), Hb grade ≥ 1(P = 0.015), platelet grade ≥ 2(P = 0.004) and pneumonia grade ≥ 2(P = 0.002) were significantly associated with OS in the TRT group. Multivariate analysis identified no factor was independent prognostic factors for OS (Table 2). For PFS, univariate analysis showed that pneumonia grade ≥ 2(P = 0.037) was significantly associated in the entire cohort. PTV (P < 0.001) and pneumonia grade ≥ 2 (P < 0.009) were significantly associated in the TRT group. Multivariate analysis indicated that PTV (P = 0.003) was independent prognostic factor (Table 3).

3.4 Safety

Treatment-related adverse events were significantly more common in patients who received TRT compared to those who did not. Hematologic toxicities, including leukopenia, lymphopenia, neutropenia, anemia, and thrombocytopenia, were all significantly more frequent in the TRT group. Lymphopenia was the most prevalent hematologic toxicity, observed in 84.97% of patients in the TRT group vs. 32.67% in the non-TRT group (p < 0.001), with ≥ grade 2 events in 67.18% vs. 11.33%, respectively. In terms of pulmonary toxicity, pneumonia was also significantly more frequent among patients receiving TRT. Any-grade pneumonia occurred in 71.31% of the TRT group vs. 17.68% in the non-radiotherapy group (p < 0.001). Grade 2 or higher pneumonia was observed in 17.83% of patients in the TRT group compared to 4.88% in the non-TRT group (p < 0.001) (Table 4).

4. Discussion

In this study, we conducted a stratified analysis of 523 patients based on molecular subtypes and treatment options. We found that the survival benefit of TRT varies depending on the type of systemic therapy. Patients receiving targeted therapy who added TRT had significantly longer PFS and OS than patients who did not. While patients receiving chemoimmunotherapy, those who received TRT had longer OS than those who did not, but there was no significant statistical difference in PFS. Further analysis revealed that, in patients receiving chemoimmunotherapy, the inclusion of TRT did not significantly affect PFS, nor did the occurrence of radiation pneumonitis or immune-related pneumonitis. The reasons for this remain to be investigated in future studies. In addition, this study also identified independent factors affecting the prognosis of targeted therapy or chemoimmunotherapy combined with TRT, namely the PTV. Other factors such as age, gender, ECOG status, and various adverse events that occurred during treatment could not be considered as independent factors affecting prognosis in this study.

TRT demonstrated significant PFS and OS benefits in patients with EGFR/ALK mutations, consistent with the mechanistic synergy between TKIs and radiotherapy. Preclinical studies have shown that EGFR-TKIs

(such as osimertinib) enhance radiosensitivity by inhibiting DNA repair pathways and promoting radiation-induced apoptosis(18). Clinically, the combination of TRT with EGFR-TKIs can delay acquired resistance and improve tumor control(16). Our data further support this observation, indicating that TRT during TKI treatment maximizes local control and systemic efficacy. On the contrary, although chemoimmunotherapy patients showed improvement in OS, TRT did not improve PFS, a phenomenon that warrants careful review. TRT may induce systemic immune activation, delaying the formation of new metastatic lesions without affecting existing lesions (therefore having a greater impact on OS than PFS), which is known as the abscopal effects(19). It is worth noting that exploratory analyses showed no differences in PFS based on pneumonia grade (P = 0.45), suggesting that radiation pneumonitis/ immune-related pneumonitis did not lead to reduced PFS. This finding contrasts with studies linking severe pneumonia to mortality(20, 21). Strict supportive care (such as early glucocorticoid intervention) in our cohort may have mitigated the risk of pneumonia-related mortality.

In the meantime, TRT increased hematological and pulmonary toxicity in all groups. The incidence of severe (≥ grade 2) lymphocytopenia was 67.18% in TRT group and 11.33% in non-TRT group. This difference is clinically significant because lymphopenia weakens antitumor immunity and is associated with poor prognosis in patients with NSCLC. The incidence of pneumonia of all grades in the TRT group was 71.31%, consistent with recent report on TRT combined with immunotherapy(22). These results provide important clinical insights. For patients receiving TKI therapy, the survival benefit of TRT outweighs the toxicity risk, provided that strict adherence to dosing restrictions (e.g., lung V20 ≤ 30%) and techniques to mitigate lymphopenia (e.g., bone marrow protection) are employed. In chemoimmunotherapy, the OS benefit of TRT supports its use in specific patient groups (such as patients with oligometastatic disease), but the risk of pneumonia requires careful patient selection, especially for patients with a history of lung disease.

Multivariate analysis identified PTV as an independent predictor of PFS in the TRT group (P = 0.003), In tumors such as cervical cancer, a larger PTV is typically associated with poorer prognosis, consistent with findings from previous study(23). This may be associated with residual tumor and increased risk of local recurrence. Larger target areas increase radiation doses to adjacent organs (such as the heart and lungs), thereby exacerbating toxic reactions and affecting treatment tolerance. It is worth noting that traditional factors (age, ECOG status, metastatic burden) did not independently predict survival, emphasizing the critical impact of technical parameters of radiotherapy (such as PTV optimization) on treatment outcomes in combination therapy.

Our study still has some limitations. First, our patients are all from a single center, lacking external validation from multiple centers. Second, unmeasured confounding factors (e.g., timing of radiotherapy) may influence treatment outcomes. Additionally, we did not differentiate between radiotherapy techniques for different patients, and combined multiple TRT techniques and fractionation regimens for analysis. In the future, our research will conduct prospective validation and confirm the OS benefit of TRT in chemoimmunotherapy through randomized trials. We will explore biomarkers, integrating circulating

tumor DNA (ctDNA) clearance or metabolomics changes, to identify patients most likely to benefit from TRT.

In metastatic NSCLC, radiotherapy synergistically interacts with targeted therapy, significantly prolonging PFS and OS. In chemoimmunotherapy, radiotherapy improves OS, though no PFS benefit is observed—this may be achieved through distant effects or delayed resistance. However, this is accompanied by increased hematological and pulmonary toxicity. Crucially, optimization of the PTV as a modifiable factor can enhance treatment efficacy. In the future, personalized radiotherapy integration strategies by molecular subtypes, tumor volume, and toxicity risk will maximize survival while maintaining quality of life.

Abbreviations

NSCLC: Non-small cell lung cancer

PFS: Progression-free survival

CI: Confidence interval

TRT: Thoracic radiotherapy

OS: Overall survival

TKI: Tyrosine kinase inhibitors

PCR: Polymerase chain reaction

NGS: Next-generation sequencing

IHC: Immunohistochemistry

3D-CRT: 3D conformal radiotherapy

IMRT: Intensity-modulated radiation therapy

HR: Hazard ratio

NR: Not reached

PTV: Planning target volume

ctDNA: circulating tumor DNA

Declarations

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Authors' contributions

Lishan Xue: Data curation, formal analysis, investigation, methodology, and writing (original draft).

Jinquan Yao: Data curation, formal analysis, investigation, methodology, and writing (original draft).

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Yuxin Geng: Data curation, formal analysis.

Ning Tang: Conceptualization and writing (review and editing).

Feifei Teng: Conceptualization and writing (review and editing).

All authors read and approved the final version of the manuscript.

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Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki.This study was waived the need for approval by the Ethics Committee of Shandong First Medical University Affiliated Cancer Hospital

Availability of data

All data supporting the findings of this study are available from the corresponding author.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Tables

Tables 1 to 4 are available in the Supplementary Files section.