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Efficacy and safety of tyrosine kinase inhibitors with thoracic radiotherapy for patients with oncogene-mutated non-small cell lung cancer: a meta-analysis

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Abstract

Background Tyrosine Kinase Inhibitors (TKIs) is an important therapy for patients with oncogene-mutated Non-Small Cell Lung Cancer (NSCLC). However, acquired resistance remains a major challenge. The efficacy of TKIs plus thoracic radiotherapy (RT) in oncogene-mutated NSCLC patients is uncertain. Therefore, we performed a meta-analysis to comprehensively evaluate the efficacy and safety of thoracic RT plus TKIs in oncogene-mutated NSCLC patients.

Methods The following databases were searched for relevant studies: PubMed, EMBASE, and Cochrane Library. Studies comparing the efficacy and safety of TKIs plus RT with TKIs alone in oncogene-mutated NSCLC patients were included in this analysis. Outcomes were median progression-free survival (mPFS), median overall survival (mOS), and incidence of adverse events (AEs). This analysis performed a subgroup analysis of the efficacy of first-line TKIs in combination with RT.

Results This meta-analysis included 12 studies with 2936 patients (n = 823 patients with TKIs plus thoracic RT, n = 2113 patients with TKIs alone). The results showed that patients who received treatment with TKIs plus thoracic RT were associated with superior mPFS and mOS than those who were treated with TKIs alone (hazard ratio [HR]: 0.42, 95% CI 0.30–0.59, $p < 0.00001$; HR: 0.56, 95% CI 0.41–0.70, $p < 0.00001$, respectively). Subgroup analyses showed that TKIs plus thoracic RT as first-line treatment was associated with better mPFS and OS (HR: 0.37, 95% CI 0.26–0.52, $p < 0.00001$; HR: 0.47, 95% CI 0.31–0.70, $p = 0.0002$, respectively). Although the combination of TKIs with thoracic RT was associated with an increased risk of total AEs (odds ratio [OR]: 1.17, 95% CI 1.06–1.29, $P = 0.002$), there was no significant difference in serious AEs (grade ≥ 3) (OR: 1.06, 95% CI 0.58–1.92, $P = 0.86$). The most frequently occurring radiation-related AEs were radiation pneumonitis, radiation esophagitis, and radiation dermatitis, with overall rates of 41.3%, 15.4%, and 11.1%, respectively. The incidence of severe radiation pneumonitis and radiation esophagitis was 4.5% and 6.2%, respectively.

Conclusions In comparison to TKIs alone, TKIs plus thoracic RT are associated with survival benefits, especially as a first-line treatment option. Although TKIs plus thoracic RT may increase the risk of total AEs, it did not increase

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the risk of severe AEs. Therefore, TKIs plus thoracic RT may be a promising therapeutic regimen for oncogene-mutated NSCLC patients.

Keywords Tyrosine kinase inhibitors, Thoracic radiotherapy, Oncogene-mutated, Non-small cell lung cancer, Meta-analysis

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide. Approximately 80% of all lung cancers are classified as non-small cell lung cancer (NSCLC) [1]. The identification of oncogene mutations in NSCLC has facilitated the implementation of personalized molecularly targeted therapies. The most common mutated genes in Chinese NSCLC patients are Epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene homologue (KRAS), and Anaplastic lymphoma kinase (ALK), with incidence rates of 45–55%, 8–10%, and 5–10%, respectively [2]. Tyrosine kinase inhibitors (TKIs) have been demonstrated to significantly improve progression-free survival (PFS) and quality of life in NSCLC patients with oncogene mutation, particularly in those with EGFR mutation [3–5]. Consequently, TKIs have become a primary treatment for NSCLC patients harboring oncogenic mutations. EGFR-TKIs monotherapy has been established as the standard first-line treatment for EGFR-mutated metastatic NSCLC patients.

In recent years, the application of TKIs has significantly impacted the therapeutic management of NSCLC with oncogene mutations. Although TKIs monotherapy represents an important treatment for NSCLC patients with oncogene mutations, the development of drug resistance represents a challenge to TKIs. Drug resistance is associated with a limited prognosis for NSCLC patients. Therefore, it is imperative to develop a treatment that is capable of delaying or preventing the emergence of drug resistance. Several preclinical studies have shown that radiotherapy (RT) may impede the emergence of drug resistance by enhancing the radiosensitivity of EGFR-TKIs [6–8]. In light of this conclusion, several single-arm trials have investigated the efficacy of EGFR-TKIs plus RT in NSCLC patients, confirming that this regimen shows promise in the treatment of NSCLC [9, 10]. Focusing on advances in randomized controlled trials (RCT), the SINDAS trial [11] (NCT02893332) evaluated the efficacy of first-line TKIs with RT in synchronous oligometastatic EGFR-mutated NSCLC. A total of 133 patients (n = 65 TKI only, n = 68 TKI with RT) were enrolled in this trial. The results showed that TKIs plus RT statistically improved PFS and OS for EGFR-mutated NSCLC compared with a first-line TKI alone. Moreover, another clinical study [12] showed a PFS of 9.0 months in the EGFR-TKIs group compared to 17.6 months in the stereotactic body radiation therapy (SBRT) group (Hazard Ratio [HR]: 0.52, 95% Confidence Interval [CI] 0.31–0.89, $P = 0.016$). The study [12] also showed that the median OS for EGFR-TKIs group was 23.2 months, compared to 33.6 months for the SBRT group (HR: 0.53, 95% CI 0.30–0.95, $P = 0.026$). It was demonstrated that the combination of SBRT significantly delayed the development of acquired resistance of EGFR-TKIs and prolonged PFS and OS in patients.

The main pattern of disease progression in NSCLC patients treated with TKIs is local progression of the primary tumor. Effective treatment for the primary tumor plays an important role in the treatment of oncogene-mutated NSCLC [13–15]. Currently, clinical studies investigating the efficacy and safety of TKIs with thoracic RT have reported disparate outcomes. The combination of TKIs and RT may result in an increased risk of adverse events (AEs). Several studies have reported that the addition of RT to EGFR inhibitors increases the risk of severe AEs. One single-arm study found a 20% probability of grade 3 and higher radiation-associated pneumonitis occurred during concurrent RT [9]. A retrospective study [16] showed that RT plus EGFR-TKIs increased the risk of mild or moderate radiation pneumonitis, but not severe radiation pneumonitis. It remains undetermined whether the risk of AEs is higher with the use of TKIs plus thoracic RT in NSCLC. Therefore, we conducted a meta-analysis to evaluate the efficacy and safety of TKIs plus thoracic RT in oncogene-mutated NSCLC.

Methods

Search strategy

This study was conducted by 2 reviewers independently according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. The PICO criteria of this meta-analysis are as follows:

Participants: participants are Non-Small Cell Lung Cancer (NSCLC) patients with oncogene mutations.

Intervention: Tyrosine Kinase Inhibitors (TKIs) combined with thoracic radiotherapy (RT).

Control: TKIs monotherapy.

Outcome: median progression-free survival (mPFS), median overall survival (mOS), and incidence of adverse events (AEs).

A comprehensive search of relevant studies was conducted in PubMed, Embase, and Cochrane Library up to February 1, 2024. The following search terms were used: "Non-Small-Cell Lung", "Non-Small-Cell Lung Carcinomas", "Carcinoma, Non-Small-Cell Lung", "Non-Small Cell Lung Cancer", "NSCLC", "Tyrosine Kinase Inhibitors", "TKIs", "Radiotherapy", "Radiation Treatment", "Radiation Therapy", and "RT". The language of the articles is limited to English. The complete search strategy is presented in the Supplementary Method 1. The authors also retrieved and reviewed the references to supplement the search results. In case of duplicate trials, only the most comprehensive and recently updated reports were included in this analysis.

Inclusion and exclusion criteria

Inclusion criteria: (1) eligible patients were histologically confirmed to have NSCLC with oncogene mutations; (2) studies evaluating the efficacy and safety of TKIs plus thoracic RT; (3) studies reporting at least one of the following outcomes: mPFS, mOS, and AEs.

Exclusion criteria: (1) single-arm trials, basic studies, case reports, systematic reviews, and duplicate publications; (2) studies that did not use TKIs plus thoracic RT as treatment in the experimental group; (3) studies that did not use TKIs monotherapy as the treatment of control groups; (4) studies that did not includ oncogene-mutated NSCLC patients. Studies that did not include mPFS, mOS, or incidence of AEs as outcomes.

Data extraction and quality assessment

Data extraction and quality assessment were conducted independently by two researchers. When multiple articles included the same patient cohort, we prioritized the article with the largest sample size and longest follow-up duration for the outcome data. The following data were extracted from the eligible studies: the first author's name, year of publication, sample size, age, oncogene mutation status, clinical stage, treatment regimen, mPFS, mOS, and treatment-related AEs. Two investigators conducted assessments of quality independently, using the Newcastle–Ottawa Scale (NOS) for retrospective studies and the Cochrane Collaboration risk of bias tool for randomized controlled trials. Any discrepancies that arose during the process of data extraction and quality assessment were resolved by a third reviewer.

Statistical analysis

All statistical analyses were performed using the Review Manager 5.4 software. The safety of combination therapy was evaluated by calculating the overall risk of grade ≥ 3 AEs and all grade AEs. A pooled odds ratio (OR) with 95% CI was used for the comparison of treatment-related AEs, while a pooled HR was used for the assessment of mOS and mPFS. The heterogeneity between studies was evaluated using Cochran's Q test and the I^2 index. The random-effect model was used when there was significant heterogeneity (I^2 values $> 50\%$) among studies; otherwise, the fixed-effect model was used to pool the OR or HR. In addition, a funnel plot and an Egger test were adopted to assess the publication bias among the included studies. All statistical tests were two-sided, and differences were considered statistically significant when $p < 0.05$.

Results

Study identification and quality assessment

A total of 989 articles were retrieved by searching three electronic databases; PubMed, Embase, and Cochrane Library. All search results were filtered and selected using Endnote. The comprehensive process of the literature review is illustrated in Supplementary Fig. 1. Following the removal of 102 repetitive articles, 887 articles were identified through a process of reading and screening based on their title and abstracts. A total of 866 documents were excluded from further consideration, primarily due to their lack of relevance to the topic under investigation or the inappropriate study type (reviews, pathology reports, in vitro studies, and meta-analyses). Of the remaining 21 studies, a total of 9 articles were excluded after a comprehensive review of the full text. The reasons for exclusion were as follows: non-controlled trials (n = 5), non-TKIs monotherapy control group (n = 1), non-oncogene mutations NSCLC patient (n = 2), and lack of sufficient research data (n = 1). A total of 12 trials [11, 12, 17–26] were ultimately in the analysis. The quality assessment of these trials is presented in Supplementary Figs. 2a, b, and 3, showing an overall low risk of bias.

Study and patient characteristics

The characteristics of the included studies are shown in Supplementary Table 1. This meta-analysis included 12 studies comprising 2936 patients, of whom 823 patients were treated with TKIs + thoracic RT while the remaining 2,113 patients were treated with TKIs alone. Of these 12 studies, 2 studies [11, 12] were randomized controlled trials (RCT), 10 studies [17–26] were retrospective studies, and patients in 7 trials [11, 12, 19, 20, 22, 24, 25] were treated with first-line TKIs alone. Except for two trials [18, 26] that did not provide specific genotyping, the remaining ten trials included patients with EGFR exon 19 and exon 21 mutations. Only Li's trial [18] included patients with ALK mutations.

Results of meta-analysis

mPFS of TKIs plus thoracic RT in oncogene-mutated NSCLC patients

To evaluate the efficacy of TKIs plus thoracic RT in oncogene-mutated NSCLC, we conducted a comparative analysis of the efficacy of TKIs with thoracic RT versus TKIs alone. A total of 10 trials [11, 12, 17, 19–25], 1349 patients were included in the analysis (n = 472 TKIs plus thoracic RT, n = 877 TKIs alone). The results of this analysis showed that patients who received TKIs plus thoracic RT were associated with superior mPFS (HR: 0.42, 95% CI 0.30–0.59; $p < 0.00001$). However, there was significant heterogeneity in the analysis ($Chi^2 = 66.01$, df = 9 [$p < 0.00001$]; $I^2 = 86\%$) (Fig. 1).

The diamond indicates best estimate of the true (pooled) outcome (with width indicating 95% CI); experimental stands for tyrosine kinase inhibitors plus radiotherapy (TKIs + RT); control stands for tyrosine kinase inhibitors only (TKIs only). Since there is a high heterogeneity, a random-effects model is used.

mOS of TKIs plus thoracic RT in oncogene-mutated NSCLC patients

A total of 2833 patients from 11 clinical trials [11, 12, 17–23, 25, 26] were included in the mOS analysis (n = 777 TKIs with thoracic RT, n = 2056 TKIs only). Overall, the pooled HR was 0.56 (95% CI 0.41–0.70; $p < 0.00001$), but the analysis showed significant heterogeneity ($Chi^2 = 39.01$, df = 10 [$p < 0.0001$]; $I^2 = 74\%$) (Fig. 2).

The diamond indicates best estimate of the true (pooled) outcome (with width indicating 95% CI); experimental stands for tyrosine kinase inhibitors plus radiotherapy (TKIs + RT); control stands for tyrosine kinase inhibitors only (TKIs only). Since there is a high heterogeneity, a random-effects model is used.

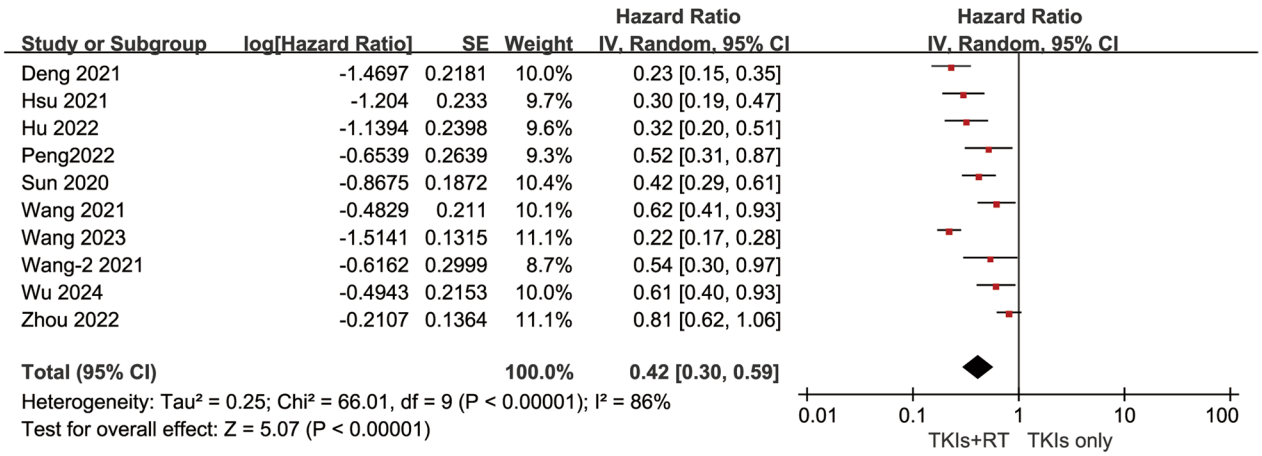

Fig. 1 Assessment of median Progression Free Survival (mPFS)

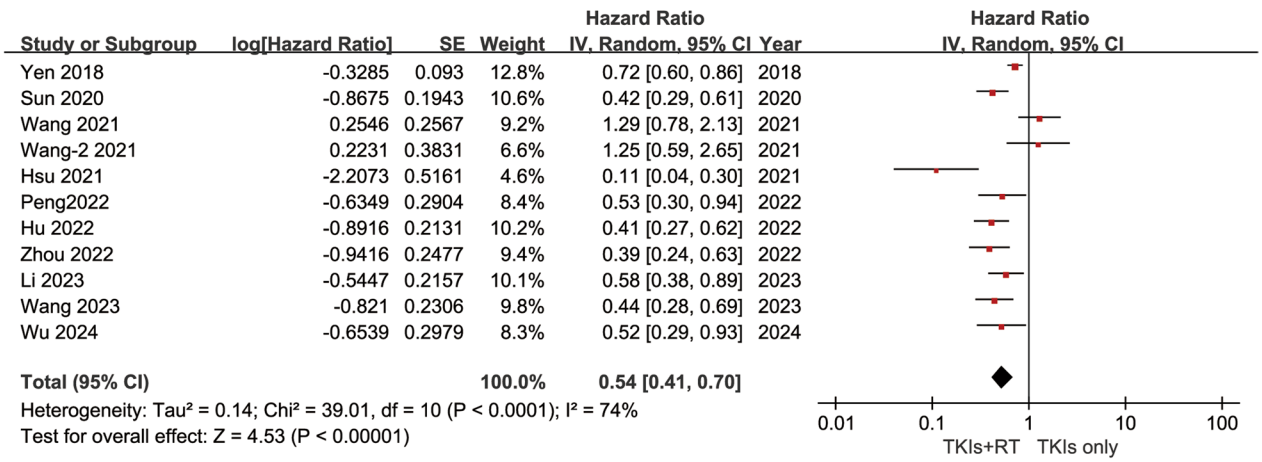

Fig. 2 Assessment of median Overall Survival (mOS)

Efficacy of first-line TKIs plus thoracic RT in oncogene-mutated NSCLC patients

To investigate the efficacy of first-line TKIs with RT in patients with oncogene-mutated NSCLC, we analyzed seven studies. The results showed that the combination of first-line TKIs and thoracic RT exhibited a HR of 0.37 for mPFS (95% CI 0.26–0.52; $p<0.00001$) and 0.47 for mOS (95% CI 0.31–0.70; $p=0.0002$). Additionally, both analyses exhibited heterogeneity ($Chi^2=27.88$, df=6 [$p<0.0001$], $I^2=78\%$ and $Chi^2=15.14$, df=5 [$p=0.010$], $I^2=67\%$, shown in Figs. 3 and 4, respectively).

The diamond indicates best estimate of the true (pooled) outcome (with width indicating 95% CI); experimental stands for tyrosine kinase inhibitors plus radiotherapy (TKIs+RT); control stands for tyrosine kinase inhibitors only (TKIs only). Since there is a high heterogeneity, a random-effects model is used.

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Adverse effects

The overall risks of all AEs and serious AEs (≥grade 3) were calculated to assess the safety of TKIs plus thoracic RT. The most common AEs were skin rash, fatigue, and anemia with incidence rates of 59.8%, 35.7%, and 32.4% respectively (Supplementary Table 2). The most common serious AEs were skin rash, elevated aminotransferase, and paronychia with incidence rates of 8.6%, 4.7%, and 1.4%, respectively (Supplementary Table 3). The analysis showed that TKIs with thoracic RT resulted in an increased risk of total AEs (OR=1.17, 95% CI 1.06–1.29, $P=0.002$, Supplementary Fig. 4) but not in severe AEs (OR=1.06, 95% CI 0.58–1.92, $P=0.86$, Supplementary Fig. 5). No significant heterogeneity in two analyses (total AEs: $Chi^2=47.16$, df=30 [$P=0.02$], $I^2=36\%$; severe AEs: $Chi^2=1.50$, df=7 [$P=0.98$], $I^2=0\%$, Supplementary Figs. 4 and 5). The most common radiation-related AEs were radiation pneumonitis, radiation esophagitis, and radiation dermatitis, with an overall risk of 41.3%, 15.4%, and 11.1%, respectively (Supplementary Table 4). The incidence of severe radiation pneumonitis and radiation esophagitis was 4.5% and 6.2%, respectively (Supplementary Table 4).

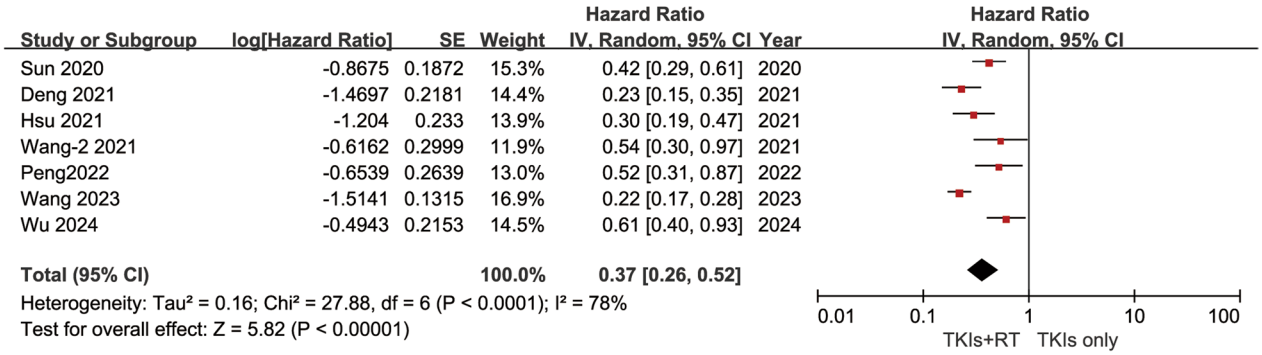

Fig. 3 Assessment of median Progression Free Survival (mPFS) of first-line treatment

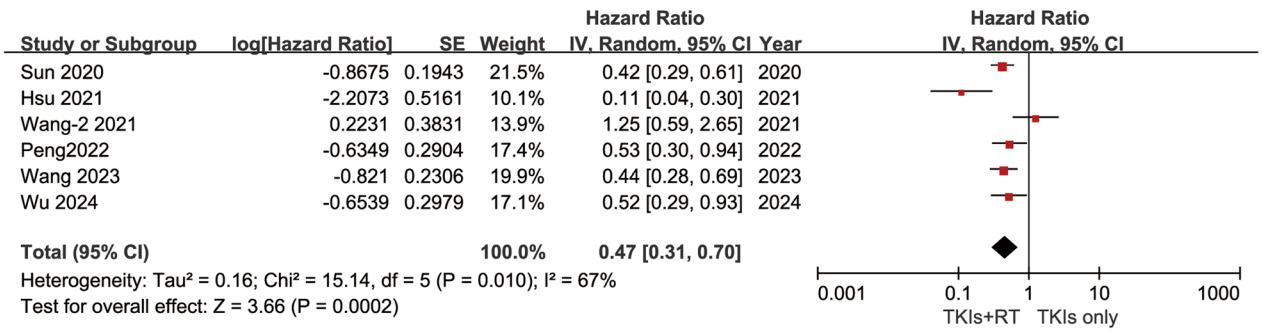

Fig. 4 Assessment of median Overall Survival (mOS) of first-line treatment

Sensitivity analysis, publication bias, and heterogeneity analysis

A sensitivity analysis via study-by-study removal demonstrated that no single study exerted a significant influence on the overall effect of the efficacy and safety endpoints, indicating that the results were stable. The Funnel plots of mOS and PFS are shown in Supplementary Figs. 6 and 7. Egger regression test results showed that mOS ($p=0.218$) and mPFS ($p=0.053$) had low potential for publication bias. Subgroup analyses by study types showed that there was heterogeneity in both RCT and retrospective studies subgroups in mOS and mPFS analysis (Supplementary Figs. 8 and 9).

Discussion

In recent years, RT has shown excellent control rates in the treatment of cancer [27, 28]. In addition to surgery and chemotherapy, RT is one of the main approaches to treating cancer patients at all pathological stages. Several studies have confirmed that brain RT can improve the survival of NSCLC patients with brain metastases [29–32]. For thoracic RT, preliminary evidence has also shown that the combination of thoracic RT and systemic medication may prolong survival and reduce the rate of local progression in NSCLC patients [9, 33–35]. It remains controversial whether patients with NSCLC who have undergone treatment with TKIs will benefit from additional thoracic RT. A single-arm trial found that TKIs plus thoracic RT for stage IIIB/IV NSCLC resulted in a 96% local control rate of thoracic tumors [36], raising hope for combination therapy of TKIs and thoracic RT. The purpose of this study was to evaluate the effect of TKIs plus thoracic RT in patients with NSCLC harboring oncogene mutations.

To our knowledge, this analysis is the first meta-analysis to evaluate the efficacy of TKIs with thoracic RT in oncogene-mutated NSCLC. We included oncogene-mutated NSCLC patients who were treated with TKIs plus thoracic RT and performed a meta-analysis to investigate the efficacy and safety of TKIs plus thoracic RT. After study identification and selection, we included 12 studies that compared the efficacy of TKIs plus thoracic RT and TKIs alone. The results showed that TKIs plus thoracic RT was associated with superior mPFS and mOS. This analysis suggests that the combination of TKIs with thoracic RT is a promising treatment for shrinking thoracic lesions in oncogene-mutated NSCLC patients. Although the combination of TKIs with thoracic RT was associated with an increased risk of total AEs, there was no significant difference in serious AEs. Although RT is associated with radiation-related AEs, the majority are grade 1–2 AEs and the risk of serious AEs is low. However, the results of this analysis are somewhat inconsistent and should be interpreted with caution because only some of the trials provided complete data on AEs.

There was heterogeneity in the analysis of mPFS and mOS. We performed subgroups analyses according to study types. The results showed that study types were not the significant factors influencing the heterogeneity in outcomes for mOS and mPFS. In particular, Li's study [18] enrolled NSCLC patients with malignant pleural effusion (MPE), which is associated with a poorer prognosis and reduction in quality of life [37, 38]. Wu's study [19] included patients who underwent primary tumor consolidation therapy, including local resection therapy. Hu's study [21] specifically included elderly patients with oligometastatic NSCLC, representing a specific population. Furthermore, the studies employed disparate RT regimens, including stereotactic body radiation therapy (SBRT), local consolidative radiation therapy (LCRT), and conventional external beam radiation therapy (EBRT).

Pathologic status is an important factor in the prognosis of NSCLC. Oligometastatic disease, characterized by a limited number of metastases (≤ 5) in a few organs (≤ 3), is an intermediate state between localized and extensively metastatic disease [39]. Oligometastatic patients tend to have better clinical outcomes than non-oligometastatic patients [40]. Several studies have shown that local treatment of metastatic sites, especially SBRT combined with systemic therapy, can significantly improve PFS and OS in patients with oligometastases [35, 41, 42]. The ASTRO/ESTRO Clinical Practice Guideline [39] provides suggestions regarding the indications and regimen of RT and highlights the clinical significance of RT for oligometastatic NSCLC patients. Although some clinical studies have found that patients with metastatic NSCLC may also benefit from local RT [23], the clinical efficacy is not as excellent as that observed in oligometastatic NSCLC patients [17, 22, 43]. Moreover, RT is preferred for oligometastatic patients because the increased number of RT sites may result in increased risks of radiation-related AEs.

It is important to consider the optimal timing for a combination of RT. Available studies have found that the median time to response (TTR) of TKIs is generally 2–3 months [44–46]. A study [47] by Li found that tumors the average tumor volume decreased obviously within 40 days. It is generally accepted that the tumor burden is lowest at the time of maximum reduction, which may be the most appropriate time for RT to the primary site [13, 23, 44, 45]. Zhou's study [23] also found that patients who received pre-progression thoracic RT had better mPFS than those who received post-progression thoracic RT and had a lower risk of radiation pneumonitis. In addition, a study [25] found that upfront RT is associated

with superior survival benefits compared to TKIs alone in patients with non-surgical stage I to III EGFR-mutated NSCLC. These studies indicate that the addition of RT at an early stage of TKIs therapy may result in better survival outcomes for NSCLC patients.

However, the majority of these trials have focused on first- or second-generation EGFR-TKIs. Third-generation EGFR-TKIs as first-line regimens have shown a significant benefit, with a median remission duration of 17.2 months [48, 49]. ALK-TKIs have been shown to be effective in patients with ALK mutations [50, 51], but there are few studies evaluating the efficacy of ALK-TKIs in combination with RT. The optimal timing for the addition of RT in patients treated with third-generation TKIs has not been studied and needs further investigation. In light of available evidences, it is advisable to consider the addition of RT after 2–3 months of first- or second-generation EGFR TKIs is recommended, especially for patients who received first-line TKIs treatment.

The most common molecular mechanism leading to acquired resistance to first- and second-generation EGFR-TKIs is the T790M mutation in EGFR exon 20. In vitro [36] and clinical [42] studies have reported that RT to primary tumors may potentially reduce the frequency of T790M mutations. However, some clinical trials have shown that the incidence of T790M mutations was not reduced in patients treated with TKIs plus RT [12, 17, 24]. The variation in outcomes may be related to the activation of other resistance pathways, such as ALK and MET mutations. Further clinical studies are required to identify the resistance mechanisms of TKIs and the mechanisms of RT in delaying resistance.

There are still limits in this analysis. First, most of the included studies were retrospective studies with small sample sizes and conducted in single centers. Despite the application of propensity score matching (PSM) and multivariate survival analysis in these studies, the bias may still be present. Second, the majority of enrolled participants were diagnosed with EGFR mutations, which are caused by the pathogenesis characteristics. Third, some trials allowed patients to receive RT for metastatic sites such as the brain and bone in addition to thoracic RT.

The challenge of drug resistance persists in the treatment of TKIs. Studies of TKIs plus RT in various populations are also ongoing. A small-sample phase II study [52] was conducted to evaluate the efficacy of EGFR TKIs in the neoadjuvant treatment of NSCLC after locally administered therapy. The findings indicated that the combination therapy (EGFR TKIs + RT) resulted in greater tumor response than TKIs alone. In addition, other trials evaluating the efficacy of TKIs in combination with RT in patients with NSCLC (NCT03256981, NCT03410043, NCT04764214) are carrying on prosperously. Currently, immunotherapy is an important alternative for NSCLC patients who have failed in TKIs therapy. Existing studies have also confirmed that RT combined with immunotherapy can provide a significant survival benefit for NSCLC patients [53–57]. However, TKIs plus immunotherapy have not achieved progress due to an increase in the incidence of AEs [58, 59]. Double-TKIs therapy has been preliminarily successful in treating NSCLC patients with acquired resistance [60, 61]. It is expected that more large-scale, multicenter, randomized controlled trials will be conducted to provide more reliable evidence for combination therapy. The combinations of TKIs and other antitumor therapies are novel therapeutic pathways deserving to be explored.

Conclusions

In comparison to TKIs alone, TKIs plus thoracic RT are associated with survival benefits, especially as a first-line treatment option. Although TKIs plus thoracic RT may increase the risk of total AEs, it did not increase the risk of severe AEs. Therefore, TKIs plus thoracic RT may be a promising therapeutic regimen for oncogene-mutated NSCLC patients.

Abbreviations

TKIs	Tyrosine kinase inhibitors
NSCLC	Non-small cell lung cancer
RT	Radiotherapy
PFS	Progression-free survival
mPFS	Median progression-free survival
OS	Overall survival
mOS	Median overall survival
AEs	Adverse events
HR	Hazard ratio
CI	Confidence interval
OR	Odds ratio
EGFR	Epidermal growth factor receptor
KRAS	Kirsten rat sarcoma viral oncogene homologue
ALK	Anaplastic lymphoma kinase
SBRT	Stereotactic body radiation therapy
MPE	Malignant pleural effusion
LCRT	Local consolidative radiation therapy
EBRT	External beam radiation therapy
TTR	Time to response
RCT	Randomized controlled trial

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13014-024-02538-y.

Additional file 1. PRISMA flow diagram. PRISMA flow diagram depicting the study identification and selection

Additional file 2. Risk of bias graph of randomized controlled trials. Quality assessment was performed by assessing various measures for each randomized controlled trials using the Cochrane Bias risk tool. Overall, these trials were considered to have a low-risk bias

Additional file 3. Risk of bias summary of randomized controlled trials. Quality assessment was performed by assessing various measures for each randomized controlled trials using the Cochrane Bias risk tool. Overall, these trials were considered to have a low-risk bias

Additional file 4. Risk of bias of retrospective studies. Quality assessment was performed by assessing various measures for each retrospective studies using the Newcastle-Ottawa Scale. Overall, these trials were considered to have a low-risk bias

Additional file 5. Assessment of total adverse events. The diamond indicates best estimate of the true outcome; experimental stands for tyrosine kinase inhibitors plus radiotherapy; control stands for tyrosine kinase inhibitors only. Since there is a low heterogeneity, a fixed-effects model is used

Additional file 6. Assessment of serious adverse events. The diamond indicates best estimate of the true outcome; experimental stands for tyrosine kinase inhibitors plus radiotherapy; control stands for tyrosine kinase inhibitors only. Since there is a low heterogeneity, a fixed-effects model is used

Additional file 7. Funnel plot of median Progression Free Survival. Funnel plot asymmetry is not obvious to median Progression Free Survival

Additional file 8. Funnel plot of median Overall Survival. Funnel plot asymmetry is not obvious to median Overall Survival

Additional file 9. Subgroup analysis of median Progression Free Survival. The diamond indicates best estimate of the true outcome; experimental stands for tyrosine kinase inhibitors plus radiotherapy; control stands for tyrosine kinase inhibitors only. Since there is a high heterogeneity, a random-effects model is used

Additional file 10. Subgroup analysis of median Overall Survival. The diamond indicates best estimate of the true outcome; experimental stands for tyrosine kinase inhibitors plus radiotherapy; control stands for tyrosine kinase inhibitors only. Since there is a high heterogeneity, a random-effects model is used

Additional file 11. Search Strategy. Literature searches were performed in PubMed, Embase and Cochrane. A detailed literature search strategy is presented in Supplementary Method 1.

Additional file 12. Characteristics of included trials. The characteristics of eligible studies, including baseline characteristics, first author's name, year of studies publication, sample size, age, oncogene mutation status, clinical stage, treatment regimen, mPFS, and mOS are listed in Supplementary Table 1

Additional file 13. Overall risk of all grades adverse events. The risk of total adverse events is listed in Supplementary Table 2

Additional file 14. Overall risk of severe adverse events. The risk of severe adverse eventsis listed in Supplementary Table 3

Additional file 15. Overall risk of radiation-related adverse events. The incidence risk of total and severe radiotherapy-related adverse reactions is listed in Supplementary Table 4.

Author contributions
Wenxia Li and Peiye Wu are co-first authors of the article. Conceptualization: Wenxia Li, Peiye Wu. Data curation: Wenxia Li, Peiye Wu. Methodology: Peiye Wu, Zhanpeng Liang. Project administration: Huatang Zhang, Cantu Fang. Software: Wenxia Li, Peiye Wu. Supervision: Huatang Zhang, Cantu Fang, Luzhen Li. Validation: Yunqi Chen, Wenjing Zhang. Writing – original draft: Wenxia Li. Writing – review & editing: Zhanpeng Liang, Peiye Wu.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable for the section.

Competing interests
The authors declare no competing interests.

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