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CRITICAL REVIEW

Treatment-Related Pneumonitis of EGFR Tyrosine Kinase Inhibitors Plus Thoracic Radiation Therapy in Patients With Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis

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Thoracic radiation therapy (RT) for non-small cell lung cancers may overcome resistance to tyrosine kinase inhibitors (TKIs). However, the risk of severe treatment-related pneumonitis (TRP) is a major concern, and the results of the combined treatment remain controversial. Therefore, we aimed to systematically review existing publications and provide a meta-analysis of TRP from a combined therapy of thoracic RT and TKIs. A systematic literature review was performed using the PubMed-MEDLINE and Embase databases to identify eligible publications. The number of severe TRP cases of grade 3 or higher was extracted and then analyzed by fixed or randomized model meta-analysis. Heterogeneity tests were performed using the I^2 and τ^2 statistics. Subgroup analyses were conducted on the types of RT and the sequence of the combined treatment. Our literature search identified 37 eligible studies with 1143 patients. Severe TRP occurred in 3.8% (95% CI, 1.8%-6.5%) of patients overall, and fatal pneumonitis occurred rarely in 0.1% (95% CI, 0.0%-0.3%). In the subgroup analysis, the severe TRP proportion was 2.3% (95% CI, 1.0%-4.1%) for patients under definitive (chemo)RT (19 studies, n = 702) versus 2.9% (95% CI, 1.3%-5.1%) for patients who received local stereotactic body RT or palliative RT (15 studies, n = 361). The severe TRP rate was 4.9% (95% CI, 2.4%-8.1%) for concurrent TKI and RT (26 studies, n = 765), which was significantly higher than TRP of 0.4% (95% CI, 0.0%-3.1%) for sequential therapy (6 studies, n = 200). Our meta-analysis showed that combined thoracic RT and epidermal growth factor receptor−TKI therapy has an acceptable risk of severe TRP and rare mortality in patients with non-small cell lung cancers. Concurrent treatment is less tolerable and should be administered with caution. Further investigations using osimertinib are required as the data on its effects are limited.

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Introduction

Lung cancer is the leading cause of cancer death worldwide.[1] Non-small cell lung cancer (NSCLC) is estimated to account for approximately 85% of all lung cancer cases, mostly initially diagnosed at advanced stages during the patient's first clinical visit, with poor prognosis.[2] Epidermal growth factor receptor (EGFR) gene mutations and anaplastic lymphoma kinase (ALK) rearrangements are the most common driver alterations in NSCLC. Phase 3 clinical trials have demonstrated higher efficacy, lower toxicities, and prolonged survival benefits from EGFR or ALK tyrosine kinase inhibitors (TKIs) compared with traditional chemotherapy.[3,4] However, most patients will inevitably develop acquired resistance to TKIs and experience disease progression after a year of target therapy.[5]

Upfront or salvage thoracic radiation therapy (TRT) to either primary tumors or oligometastatic sites may potentially overcome TKI resistance, and a synergistic effect has been demonstrated in the phase III SINDAS trial with an extended time of tumor control, improved survival, and tolerable adverse events.[6] The National Comprehensive Cancer Network guidelines for NSCLC recommend definitive therapy along with systematic therapy for selected patients with advanced NSCLC when aggressive thoracic treatment is feasible. In addition, local therapy can be considered to treat limited metastases and continue with the current TKI therapy after the progression of advanced NSCLC with driver mutations.[7] However, in the real world, physicians do not commonly use TRT) as recommended, and available data from combined treatment are also much less than data from TKI therapy alone. The potentially increased risk of treatment-related pneumonitis (TRP) could be the top concern when adding upfront and salvage thoracic RT to first-line TKI treatment.[8,9]

Radiation pneumonitis (RP) is a common and critical dose-limiting toxicity that occurs after RT to the lungs.[10] Drug-induced interstitial lung disease (ILD) is also a typical adverse event in patients with NSCLC treated with various types of TKI.[11] The combination of RT and TKIs is suspected to cause overlapping lung toxicities. However, current publications are controversial regarding the safety of TRP. Our previous study found higher lung computed tomography intensity in patients treated with EGFR-TKIs followed by stereotactic body RT (SBRT) than in those treated with SBRT alone.[12] A few studies have reported that adding thoracic RT to TKI therapy can lead to a high incidence of severe or fatal TRP, even when the RT doses to the lungs are within acceptable limits.[8,9,13] However, several prospective trials did not observe any severe pneumonitis when combining RT with TKIs.[14-17] In this study, we aimed to systematically review existing publications and conduct a meta-analysis assessing the risk of severe TRP in patients with NSCLC who underwent combined thoracic RT and TKI therapy.

Methods and Materials

Systematic review

This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42023417191). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[18] were followed as shown in Appendix E1. A systematic literature review was performed using the PubMed-MEDLINE and Embase databases from the first record available since their inception to March 31, 2023. We also manually reviewed relevant references from the search results and other sources to identify potentially missed studies. The full search terms for each database are provided in Appendix E2. Articles retrieved from the search strategy and manual sources were imported into citation manager software to remove duplicates, and the retrieved studies were screened by assessing titles and abstracts based on eligibility criteria. Potential articles were further assessed by analyzing the full text.

Study population

The eligibility criteria included the studies with (1) confirmed NSCLC, (2) patients who received thoracic RT and TKIs, and (3) patients with pneumonitis reported. Studies were excluded if (1) there was no description of the number of patients who received thoracic RT and TKIs; (2) there was an uncertain number or grade for the target patients who developed pneumonitis; (3) the study was unfinished or unpublished; (4) there were driver alterations other than EFGR or ALK mutations; (5) the study was a case report; (6) the record had an abstract only with no full-text publication; or (7) the publication was not in English.

Thoracic RT was defined as the use of high-energy photon beams to treat lung tumors or mediastinal lymph nodes. The EGFR- or ALK-TKIs used in the studies included gefitinib, erlotinib, icotinib, afatinib, osimertinib, dacomitinib, crizotinib, alectinib, brigatinib, lorlatinib, and ceritinib. The concurrent use of TKIs and RT was defined as the 2 types of treatment administered on the same day. The sequential treatment was defined as TKIs given to patients before or after RT with various time intervals. For some studies that did not report the exact time between the 2 types of treatment, we identified the treatment sequence based on the definitions in their paper, such as the descriptions of concurrent or sequential treatment or 1 treatment followed by another. The endpoint of this review was grade 3 or higher TRP. Although TRP refers to inflammation of the lung tissue caused by any kind of treatment after excluding cancer progression and infectious causes, here we only focused on RP and TKI-induced ILD. The term "ILD" is often used interchangeably with the term "pneumonitis" in patients with cancer who develop drug-related lung toxicity. We did not distinguish RT- or TKI-induced pneumonitis because it

can be challenging to identify specific causation in patients who received combined thoracic RT and TKIs.

Data extraction

The data extracted from the selected publications included the first author's name, study year, journal, study design, tumor type, number of total patients, number of eligible patients, stage, driver mutation percentages, treatment regimens, sequence of treatment, TKI type and dose, dose fractionation of RT, time interval between TKI and RT, median follow-up time, toxicity grading criteria, and the number and grade of severe pneumonitis cases. Eligible studies with missing data were recorded as having no record in the spreadsheet. Only the pneumonitis data were pooled and analyzed using a randomized or fixed model meta-analysis.

The search for publications and data extraction were independently conducted and reviewed by 2 coauthors (Y. M., H.S.) using Microsoft Excel spreadsheets. Disagreements between individuals were further discussed with another coauthor (S.W.) until a consensus was reached.

Quality control and risk of bias assessment

The quality of the included studies was assessed using the modified Newcastle-Ottawa scale[19] for noncomparative studies, which contains 8 questions in 3 scale sections, including the selection of 4 stars, comparability of 2 stars, and exposure of 3 stars. However, there was no comparison group in this review, and the 2 questions regarding the comparison and controls were removed. The modified Newcastle-Ottawa scale included 2 sections with 6 questions. The modified scale was set to 2 stars for each question. According to a total score of 12 stars, 9 to 12, 6 to 8, and less than 6 stars were considered high, medium, and low quality, respectively (Appendix E3). Discrepancies were resolved by consensus among all the coauthors.

Subgroup analysis

RT involves various doses and fractions, which can lead to different risks of RP. The concurrent use of TKIs and RT may also increase the risk of TRP compared with sequential therapy with a time interval. Subgroup analyses were performed for different types of RT and the time intervals of combined treatment. Subgroup analysis stratified study designs were conducted because retrospective studies may inherently consist of unknown selection biases affecting the overall pooled risk of TRP.

Statistical considerations

Statistical heterogeneity among the included studies was analyzed using I^2 and τ^2 statistics.[20] The potential heterogeneity was defined as an I^2 larger than 50% or τ^2 test P value less than .1. TRP event rates and their corresponding 95% CIs were estimated using fixed effects or random effects model meta-analysis according to heterogeneity test. Forest plots were constructed to visualize the data for each study. Sensitivity analysis was used to estimate the TRP proportion and I^2 values were compared by iteratively omitting each study from the total count. A funnel plot was constructed to provide a visual aid for identifying outliers and publication bias. Statistical analyses were performed using the statistical software R version 4.2.3 (R Foundation for Statistical Computing) with the packages meta and metafor.[21]

Results

Study selection and characteristics

The literature search yielded 5159 relevant studies. After multilayered screening, this systematic review and meta-analysis included 37 eligible studies published from March 2008 to January 2023, comprising 1143 patients with NSCLC (Fig. 1).[6,8,9,13-17,22-50] A typical reason for excluding studies involving patients undergoing RT and TKI treatment was the lack of reporting or uncertain numbers of severe TRP in these patients.[51-54] Two studies involving patients with ALK-mutated NSCLC treated with crizotinib were excluded in further analysis because of the limited sample size and uncertain numbers of TRP in patients treated with EGFR-TKIs.[55,56] All selected patients had NSCLC and underwent combined thoracic RT and EGFR-TKI treatment. Table 1 summarizes the

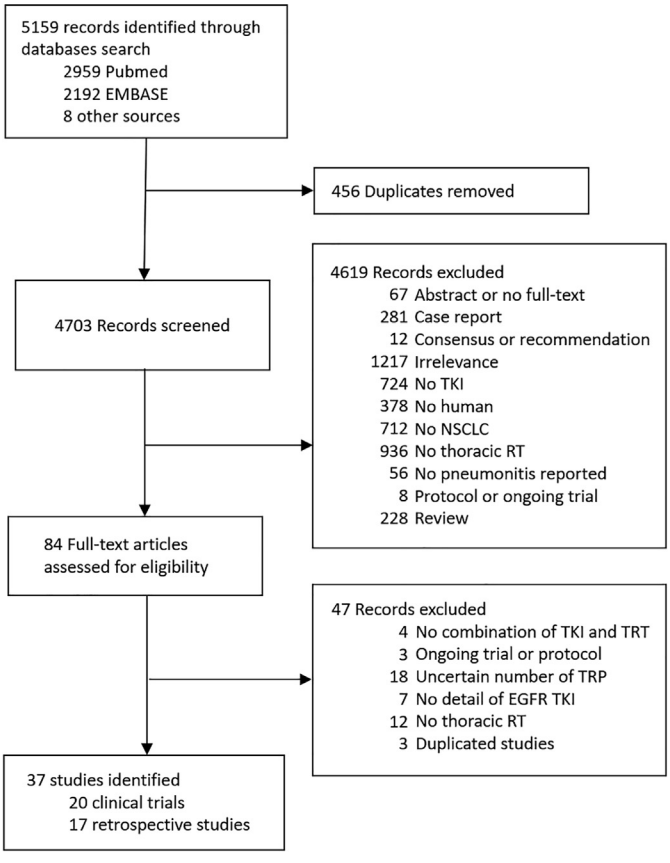

Fig. 1. Study selection flow diagram.

Table 1 Characteristics of involved studies

Year	First author	Study design	Total pts	Eligible pts	Stage	Driver mutation	TKI	RT	Sequence and time interval
2008	Stinchcombe[24]	Phase 1	23	23	III	NR	Gefitinib 250 mg, QD	60-74 Gy/30-37 fx	Concurrent, 0
2008	Choong[22]	Phase 1	34	34	III	NR	Erlotinib 50-150 mg, QD	66 Gy/33 fx	Concurrent, 0
2008	Kelly[23]	Phase 3, randomized	543	107	III	NR	Gefitinib 250 mg, QD	61 Gy/33 fx	Sequential, NR
2010	Ready[26]	Phase 2	60	60	III	EGFR: 28.9% (13/45) KRAS: 15.6% (7/45)	Gefitinib 250 mg, QD	66 Gy/33 fx	Concurrent, 0
2010	Center[25]	Phase 1	16	12	III	NR	Gefitinib 250 mg, QD	70 Gy/35 fx	Concurrent, 0
2011	Okamoto[27]	Retrospective	9	7	III	EGFR: 16.7% (1/6)	Gefitinib, 250 mg, QD	60 Gy/30 fx	Concurrent, 0
2011	Rothschild[28]	Phase 1	14	14	III	NR	Gefitinib, 250 mg, QD	63 Gy/34 fx	Concurrent, 0
2011	Wang[29]	Prospective	26	26	III/IV	NR	Gefitinib 250 mg, QD; erlotinib 150 mg, QD	70 Gy/30 fx; 56-72.8 Gy/10-13 fx; 30-51 Gy/10-17 fx	Concurrent, 0
2012	De Ruysscher[30]	Phase 2	39	1	IV	NR	Erlotinib (unknown dose)	Unknown dose	Sequential, NR
2013	Yu[32]	Retrospective	18	2	IV	EGFR: 100%	Erlotinib (unknown dose)	SBRT; conventional RT (unknown dose)	Sequential, <1 month
2013	Conforti[31]	Retrospective	15	5	III/IV	EGFR: 75% (9/12)	Erlotinib 150 mg, QD; gefitinib 250 mg, QD	SBRT (unknown dose)	Concurrent, 0
2014	Casal Rubio[14]	Phase 1	66	66	III	NR	Erlotinib 150 mg, QD	Conventional RT (median 61.2 Gy)	Sequential, 4-6 weeks
2014	Wang[34]	Retrospective	14	14	III/IV	NR	Gefitinib 250 mg, QD	SBRT: 45-60 Gy/3 fx	Concurrent, 0
2014	Iyengar[33]	Phase 2	24	14	IV	0% (0/13)	Erlotinib 150 mg, QD	19 Gy/1 fx; 27-33 Gy/3 fx; 40 Gy/5 fx	Concurrent, 0
2014	Zhuang[8]	Retrospective	24	24	III/IV	NR	Erlotinib 150 mg, QD	46-66 Gy; 1.8-2.1 Gy/fx	Concurrent, 0
2015	Lilenbaum[36]	Phase 2	78	75	III	NR	Erlotinib 150 mg, QD	66 Gy/ 33 fx	Concurrent, 0
2015	Komaki[35]	Phase 2	48	46	III	EGFR: 10.8% (4/37)	Erlotinib 150 mg, QD	63 Gy/35 fx	Concurrent, 0
2016	Gomez[37]	Phase 2, randomized	74	2	IV	EGFR (n = 2)	Erlotinib 100 mg, QD	60-70 Gy/30 fx	Concurrent, 0
2016	Martínez[38]	Retrospective	90	60	III	NR	Erlotinib 150 mg, QD	66 Gy/30 fx	Concurrent, 0
2017	Chan[39]	Retrospective	50	18	IV	EGFR: 100%	Osimertinib 80 mg, QD; first gen TKIs	50-60 Gy/3-5 fx	Sequential, 1 day

(*Continued*)

Table 1 (*Continued*)

Year	First author	Study design	Total pts	Eligible pts	Stage	Driver mutation	TKI	RT	Sequence and time interval
2018	Xu[40]	Retrospective	145	59	IV	EGFR: 100%	Gefitinib 250 mg, QD;erlotinib 150 mg, QD; icotinib 125 mg, TID; osimertinib (unknown dose)	60 Gy/30 fx; 45 Gy/15 fx; 30-37.5 Gy/5 fx; 26-33 Gy/3 fx; 21-27 Gy/1 fx	NR
2019	Weiss[15]	Phase 2	25	15	IV	EGFR: 100%	Erlotinib 150 mg, QD	21 Gy/5 fx	Concurrent or sequential, 0-3 day
2019	Zheng[41]	Phase 2	10	10	IV	EGFR: 100%	Erlotinib 150 mg, QD; gefitinib 250 mg, QD	54-60 Gy/27-30 fx	Concurrent, 0
2020	Santarpia[42]	Retrospective	36	10	III/IV	EGFR: 100%	Gefitinib 250 mg, QD	SBRT or hypo-fractionated RT (unknown dose)	Concurrent, 0
2020	Fu[16]	Phase 2	29	28	III	EGFR: 46.2% (6/13)	Gefitinib 250 mg, QD	54-60 Gy/27-30 fx	Concurrent, 0
2021	Xing[45]	Phase 2, randomized	40	18	III	EGFR: 100%	Erlotinib 150 mg, QD	60 Gy/30 fx	Concurrent, 0
2020	Jia[9]	Retrospective	11	11	III/IV	EGFR: 100%	Osimertinib 80 mg, QD	64-60 Gy/32-30 fx; 50 Gy/25 fx; 60 Gy/12-15 fx; 50 Gy/10 fx; 30 Gy/15 fx	Concurrent, 0
2021	Akamatsu[43]	Phase 2	28	27	III	EGFR: 100%	Gefitinib 250 mg, QD	64 Gy/32 fx	Concurrent, 0
2021	Xu[46]	Retrospective	45	45	III	EGFR: 44% (20/45)	Gefitinib, icotinib, erlotinib (unknown dose)	34-66 Gy (conventional fx)	Concurrent, 0
2021	Wang[44]	Retrospective	46	45	III/IV	EGFR: 100%	Gefitinib, erlotinib, osimertinib, icotinib, afatinib (unknown dose)	70 Gy/10 fx; 60 Gy/8 fx; 50 Gy/5 fx	Concurrent, 0
2023	Wang[6]	Phase 3, randomized	133	68	IV	EFGR 100%	Gefitinib 250 mg, QD;erlotinib 150 mg, QD; icotinib 125 mg, TID	25-40 Gy/5 fx	Concurrent, 0
2022	Wei[50]	Retrospective	79	79	IV	EGFR: 100%	Gefitinib, icotinib, erlotinib, osimertinib (unknown dose)	SBRT (unknown dose)	NR
2022	Shi[17]	Phase 2	41	41	IV	EGFR: 100%	Icotinib 125 mg, TID; gefitinib 250 mg, QD	40-60 Gy/5-8 fx	Concurrent, 0

(*Continued*)

Table 1 (*Continued*)

Year	First author	Study design	Total pts	Eligible pts	Stage	Driver mutation	TKI	RT	Sequence and time interval
2022	Lu[49]	Retrospective	45	9	IV	EGFR: 100%	Gefitinib 250 mg, QD;e rlotinib 150 mg, QD; icotinib 125 mg, TID	Median BED10 67.5 Gy	NR
2022	Aredo[47]	Retrospective	6	6	III	EGFR 100%	Erlotinib; osimertinib (unknown dose)	CRT (unknown dose)	Sequential, NR
2022	Deng[48]	Retrospective	113	46	IV	EGFR: 100%	Icotinib, 125 mg, TID	60-66 Gy/30-33 fx (n = 8); 60-66 Gy in 3-4 Gy/fx (n = 38)	Concurrent, 0
2023	Smith[13]	Retrospective	16	16	IV	EGFR: 100%	Osimertinib 80 mg, QD	11 Gy/1 fx; 18 Gy/3 fx; 12.5 Gy/4 fx; 8-10 Gy/5 fx; 3-6.5 Gy/10 fx; 2.5 Gy/11 fx	Concurrent, 0 (n = 14); sequential, 1 day (n = 1), 2 days (n = 1)

Abbreviations: BED = biologically equivalent dose; CRT = conformal radiation therapy; EGFR = epidermal growth factor receptor; fx = fraction; KRAS; Kirsten rat sarcoma virus; NR = no record; QD = once a day; RT = radiation therapy; SBRT = stereotactic body RT; TID = three times a day; TKI = tyrosine kinase inhibitor.

basic characteristics of the included studies. Twenty publications were prospective clinical trials[6,14-17,22-26,28-30,33,35-37,41,43,45] and 17 were retrospective studies.[8,9,13,27,31,32,34,38-40,42,44,46-50] Only 2 out of 37 studies did not include patients treated with first generation EGFR-TKIs,[9,13] and 7 papers comprised patients under osimertinib.[9,13,39,40,44,47,50] The patients with stage III NSCLC were generally prescribed 60 Gy or higher definitive (chemo)RT, whereas the metastatic NSCLC mostly received first-line TKIs combined with upfront or salvage local RT to tumor sites. Twenty-six studies delivered TKI and TRT concurrently with no time interval,[6,8,9,16,17,34-38,41-46,48] and 6 studies had patients under sequential treatment at various timespans.[14,23,30,32,39,47] Two studies had mixed timing of 2 types of treatment,[13,15] and 3 studies did not report their treatment sequence.[40,49,50] The Common Terminology Criteria for Adverse Events was used to grade the severity of TRP in 28 studies,[6,8,9,13-17,22-26,28-30,32-35,37-39,41,42,45,46,49] but 9 studies did not report their grading system about toxicities.[27,31,36,40,42-44,48,50]

Overall incidence of TRP

All 37 eligible studies reported grade 3 to 5 severe pneumonitis in 58 (5.1%) out of 1143 patients, of which grade 5 fatal TRP occurred in 7 patients (0.6%). The incidence of severe pneumonitis ranged from 0% to 45.5% among studies. Based on a random effects meta-analysis, the overall proportion of severe TRP was 3.8% (95% CI, 1.8%-6.5%) (Fig. 2). The incidence of grade 5 pneumonitis had an overall proportion of 0.1% (95% CI, 0.0%-0.3%) (Fig. 3). Between-study heterogeneity of severe TRP was considerable when pooled among 37 studies (I^2 = 68%), but there was no heterogeneity found with the specific endpoint of grade 5 TRP (I^2 = 0%).

Subgroup analysis

When separating patients by different RT types and dose fractionations, 19 studies included 702 patients who received definitive (chemo)RT,[14,16,22-29,35-38,43,45-48] and 15 studies contained 361 patients who received other RT including local SBRT and palliative RT.[6,13,15,17,30-34,39-42,49,50] The rate of severe TRP in the curative (chemo)RT population ranged from 0% to 16.7%, with proportion of 2.3% (95% CI, 1.0%-4.1%). In the local radical or palliative RT population, the proportion of patients with severe TRP was 3.6% (95% CI, 0.5%-9.6%) (Fig. 4A). There was no significant difference in the risk of TRP between the 2 types of thoracic RT. To investigate the time interval between TKI and RT, we found a severe TRP proportion of 4.9% (95% CI, 2.4%-8.1%) in the subgroup of 26 studies involving patients (n = 765) under concurrent treatment, which is significantly higher than the corresponding severe TRP proportion of 0.4% (95% CI, 0.0%-3.1%) in the 6 studies with patients (n = 200) under sequential treatment at various time intervals (Fig. 4B). The severe TRP proportions were

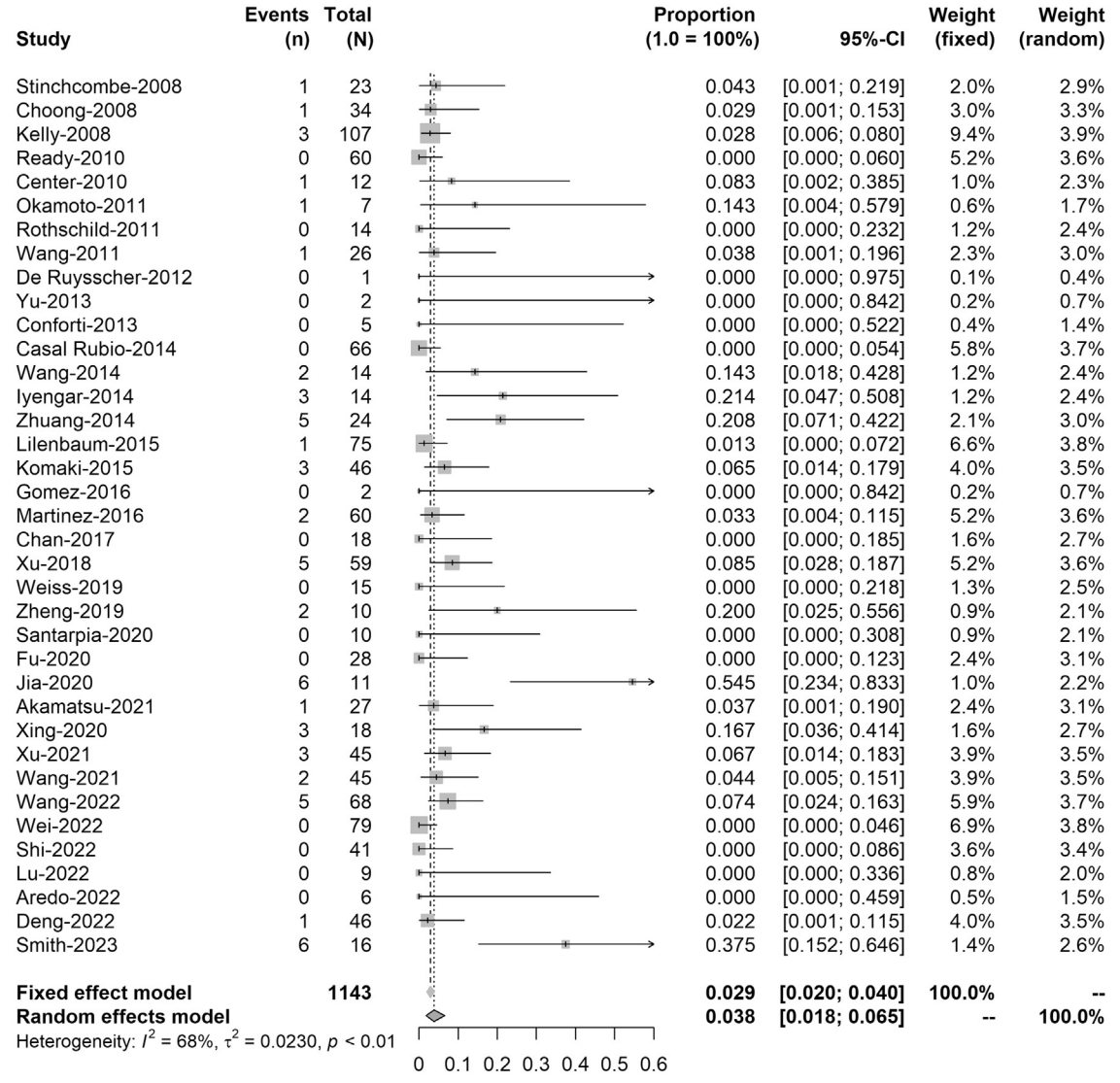

Fig. 2. Forest plot of the meta-analysis for grade 3 or higher treatment-related pneumonitis from all included studies.

2.5% (95% CI, 0.9%-4.9%) and 5.6% (95% CI, 1.5%-11.9%) in the 20 prospective trials (n = 687) and 17 retrospective studies (n = 456), respectively (Appendix E4, Fig. E1). We were unable to stratify the chemotherapy and osimertinib to evaluate the effect on the risk of TRP because of a lack of individual patient data. A summary of patient population and TRP results in each subgroup is provided in Appendix E4, Table E1.

Heterogeneity and inconsistency assessment

Nineteen studies involved unselected patients with NSCLC with unknown or negative EGFR mutations, which is not typical of patients currently undergoing TKI therapy.[8,14,16,22-31,33-36,38,46] Therefore, we assessed a median or low quality in the selection score of these studies, because they may not accurately represent average real-world patients. Details of the quality assessment of each study were provided in Appendix E4, Figure E2. Funnel plots showed visual asymmetry of grade 3 or higher TRP in 2 studies (Fig. 5A),[9,13] and asymmetry of grade 5 TRP in 1 study, which was distinct from the other studies (Fig. 5B).[8] Interestingly, only these 3 retrospective studies in our review had a primary endpoint of pneumonitis, whereas the remaining 34 papers had other objectives. The results from these 3 outlier studies suggested a publication bias toward a higher reported risk of pneumonitis. A sensitivity analysis that iteratively omitted 1 study at a time demonstrated that no specific study disproportionately affected the results of the meta-analysis (Appendix E4, Fig. E3). However, the estimated heterogeneity could be reduced after excluding 3 outlier studies (I^2 from 68%-52%). The overall severe TRP results from a subgroup of 34 studies without outliers had a TRP proportion of 2.5% (95% CI, 1.2%-4.2%) (Appendix E4, Fig. E4). The subgroup of concurrent TKI and TRT studies without outliers had a severe TRP rate of 3.5% (95% CI, 1.8%-5.7%), as shown in Appendix E4, Figure E5.

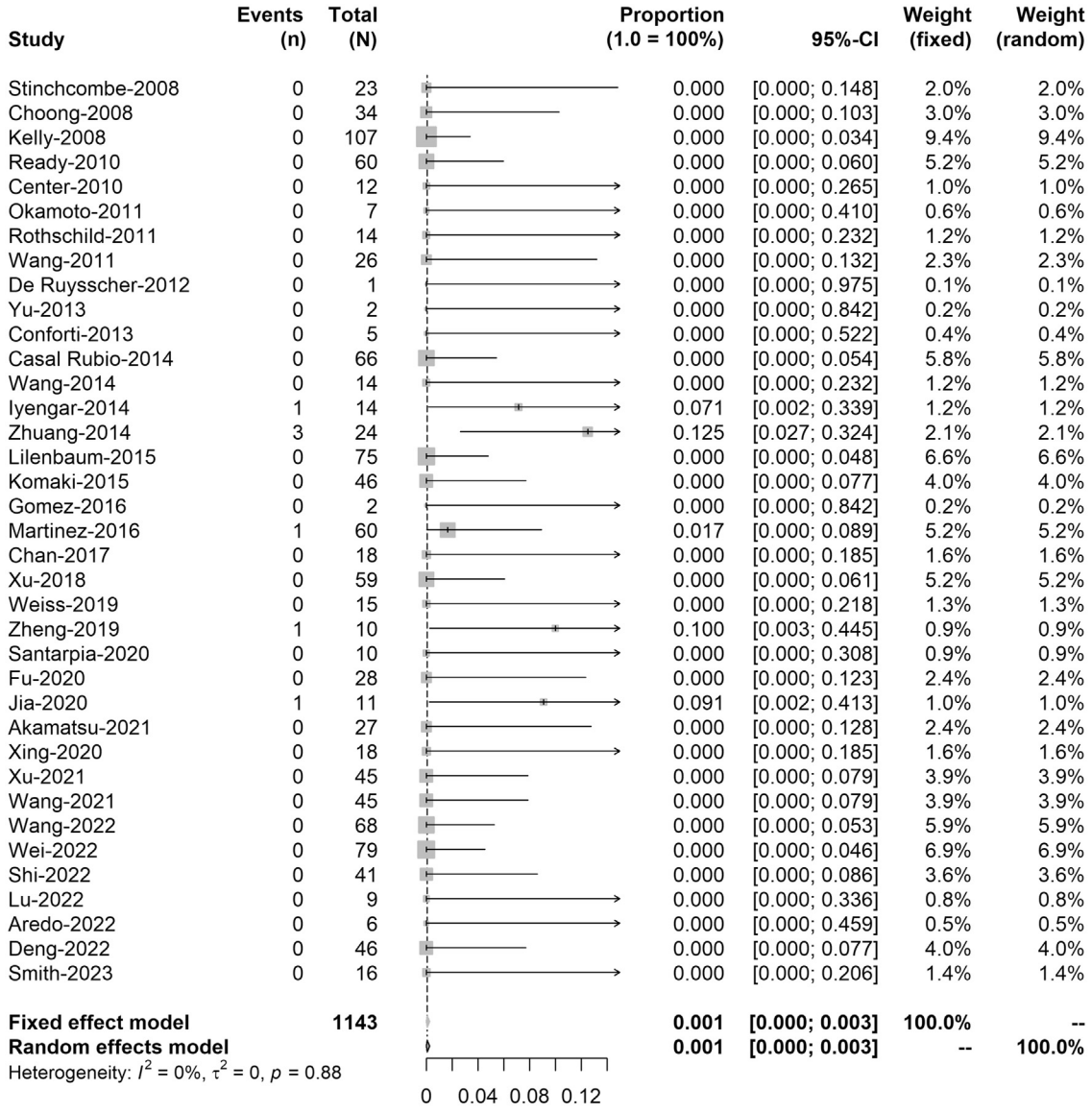

Fig. 3. Forest plot of the meta-analysis for grade 5 fatal treatment-related pneumonitis from all included studies.

Discussion

We systematically reviewed existing publications on NSCLC treated with thoracic RT and TKIs. The meta-analysis results suggested a generally acceptable 3.8% rate of severe TRP and a rare fatal TRP event with this combined treatment. To the best of our knowledge, this is the first systematic review focusing on severe TRP treated with a combination of thoracic RT and TKIs. Clinicians may be less concerned about severe pneumonitis when implementing upfront or salvage thoracic RT with TKIs in patients with NSCLC.

ILD has a low incidence but occasionally causes fatal TKI-induced pneumonitis. In some large-scale reports, the incidence of ILD induced by gefitinib was up to 5.7%, with a high mortality rate in Asian patients.[57,58] Based on a recent network meta-analysis, osimertinib-induced ILD was found to be associated with a higher risk than other EGFR-TKIs.[11] The FLAURA trial found ILD in 4% of patients treated with osimertinib.[59] A recent real-world multicenter cohort study in Japan reported a grade 3 or higher pneumonitis induced by first-line osimertinib in 21 (4.6%) out of 452 patients.[60] Our meta-analysis showed a severe TRP rate of 3.6% (95% CI, 0.5%-9.6%) in a subgroup of 361 patients treated with palliative or salvage thoracic RT, which suggested a comparable pneumonitis rate compared with historical ILD results of first-generation TKIs or osimertinib alone.

Clinically significant symptomatic RP occurs in approximately 5% to 50% of patients with lung cancer.[61] The phase 3 trial Radiation Therapy Oncology Group (RTOG) 0617 reported grade 3 or higher RP in 8 out of 285 patients (2.8%) treated with concurrent chemoRT with doses of 60 and 74 Gy.[62] In another phase 3 PROCLAIM trial, severe

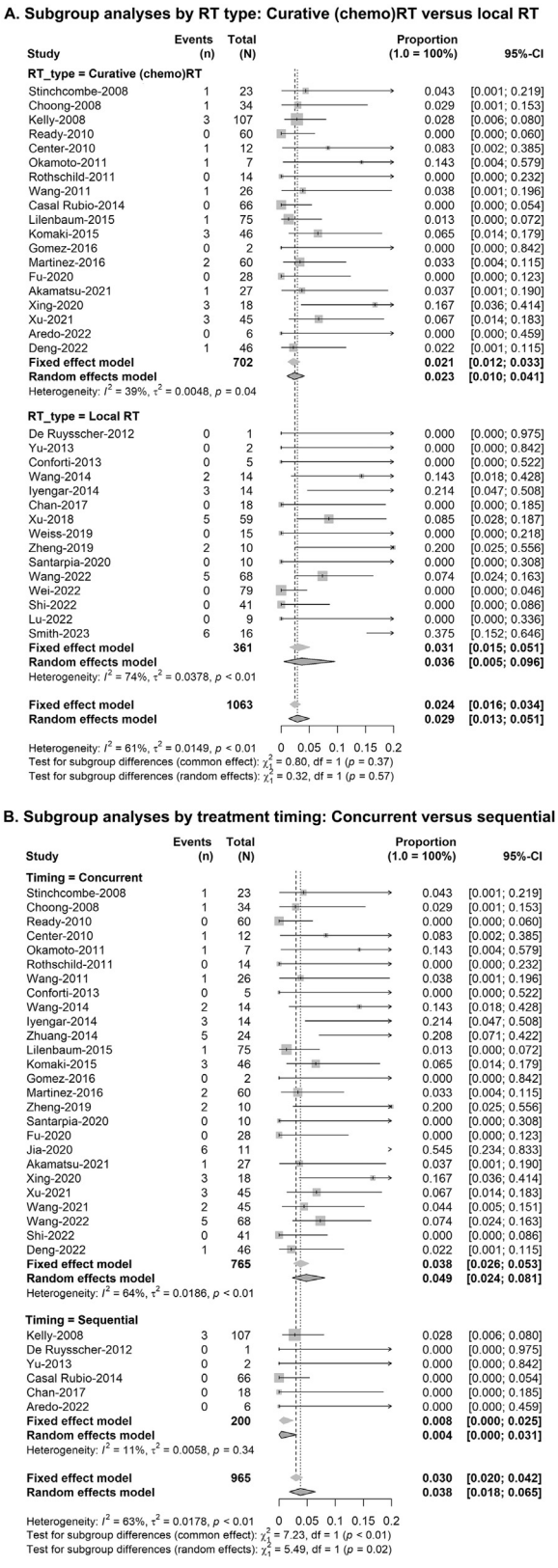

Fig. 4. Forest plot of the meta-analysis for grade 3 or higher treatment-related pneumonitis in patients by (A) RT type including curative (chemo)RT versus other RT (including stereotactic body RT and palliative RT), and (B) treatment timing of concurrent therapy versus sequential combination of tyrosine kinase inhibitor and RT. *Abbreviations:* RT = radiation therapy.

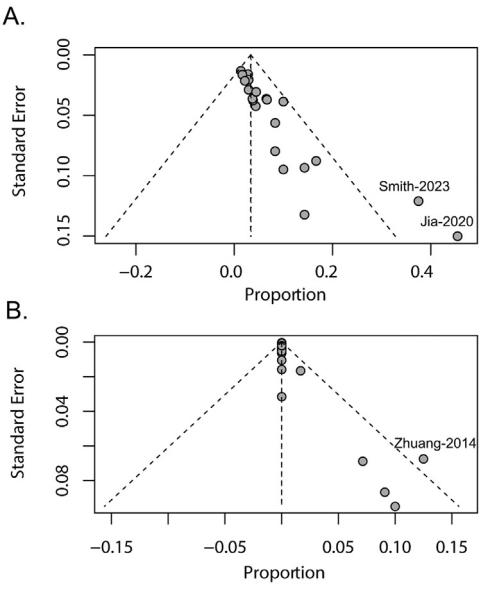

Fig. 5. Funnel plots of (A) grade 3 and 4 severe treatment-related pneumonitis and (B) grade 5 fatal pneumonitis in all included studies.

RP events were observed in 1.8% and 2.6% out of a total of 555 patients in 2 treatment arms with RT doses from 60 to 66 Gy.[63] Our meta-analysis found that a subgroup of studies employing definitive (chemo)RT combined with TKI treatment had an overall proportion of grade 3 or higher pneumonitis of 2.3% (95% CI, 1.0%-4.1%), which was similar to the RP results of the RTOG 0617 and the PROCLAIM trial. Furthermore, in terms of local RT-induced pneumonitis, our prior pooled analysis of 88 studies found an incidence of 2.2% severe RP in patients with NSCLC treated with SBRT.[64] In another retrospective study, we analyzed 339 patients with early-stage and locally recurrent NSCLC who received lung SBRT. Severe RP was found in 5.3% of patients.[65] These results were comparable with the severe pneumonitis rate of 3.6% (95% CI, 0.5%-9.6%) in the current meta-analysis in the similar RT subgroup under local radical or palliative RT. Based on our meta-analysis, the addition of TKI treatment may not substantially increase severe TRP toxicity associated with either definitive (chemo)RT or local thoracic RT.

The optimal timing for adding thoracic RT to TKI therapy remains unknown. Our review included 26 studies with patients (n = 765) treated with concurrent TKI and RT and 6 studies conducting sequential treatment (n = 200). The subgroup meta-analysis on treatment sequence revealed a higher rate of severe TRP with concurrent delivery than with sequential therapy (4.9% vs 0.4%). Unfortunately, individual clinical characteristics and toxicities were not reported in each study, preventing us from conducting a multivariate analysis to determine whether concurrent delivery was an independent hypersensitive factor. Despite this, most studies reported a relatively low or no incidence of pneumonitis after concomitant therapy.[6,16,17,22,26,28,31,36,38,42,43,48] The proportion of severe

pneumonitis was acceptable at 3.5% (95% CI, 1.8%-5.7%) in the concurrent delivery subgroup after excluding 2 outlier studies detected in the funnel plots. These data suggested that clinicians may not need to be overconcerned about overlapping lung toxicities. But still, considering the significantly higher rate of severe TRP found in concurrent treatment and that the average half-life of most TKI elimination is estimated at around 48 hours,[66] withholding TKI treatment for 2 to 4 days before initiation of RT may be a reasonably cautious strategy for patients potentially at high risk of TRP.

We recognize that this meta-analysis has several limitations. First, this review included retrospective studies, and they may be susceptible to selection bias, especially regarding the 3 outlier studies identified by the funnel plots. These 3 studies were conducted at a single institution with a small sample size, had a primary endpoint of pneumonitis, and reported an exceptionally high incidence of severe pneumonitis. We suspected that the investigators might have observed some cases of severe pneumonitis first and then generated the hypothesis of an increased risk from combined treatment. Thus, our meta-analysis may have overestimated the risk of TRP because of a potential reporting bias. Second, we did not have access to the data of individual patients, including the characteristics and details of the treatment. Association analysis of potential risk factors and assessment of confounding variables were not feasible in the current meta-analysis. Third, osimertinib is currently the standard of care of first-line treatment for patients with advanced NSCLC harboring common EGFR mutations, but the majority of the data in our review were from first-generation TKIs. The risk of TRP in patients treated with a combination of TRT and simultaneous osimertinib treatment requires further investigation. We are awaiting results from the ongoing trial NORTHSTAR (NCT03410043) assessing RT combined with osimertinib in advanced EGFR-mutated NSCLC and the LAURA trial (NCT03521154) investigating osimertinib after chemoradiation in patients with unresectable stage III EGFR-mutated NSCLC.

Conclusion

Our meta-analysis indicated that the combination of TKI with thoracic RT has an overall acceptable risk of severe TRP and rare mortality in patients with NSCLC. Concurrent treatment has a higher TRP toxicity rate than sequential therapy and should be used with caution. Data on osimertinib are lacking and require further investigation.

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