

Efficacy and Safety of Radiotherapy Plus EGFR-TKIs in NSCLC Patients with Brain Metastases: A Meta-Analysis of Published Data



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Abstract

Background: The role of radiotherapy (RT) combined with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) in non-small cell lung cancer (NSCLC) patients with brain metastasis (BM) remains controversial. Therefore, we conducted a meta-analysis to comprehensively evaluate the efficacy and safety of RT plus EGFR-TKIs in those patients. **Materials and Methods:** Relevant literatures published between 2012 and 2017 were searched. Objective response rate (ORR), disease control rate (DCR), overall survival (OS), intracranial progression-free survival (I-PFS) and adverse events (AEs) were extracted. The combined hazard ratios (HRs) and relative risks (RRs) were calculated using random effects models. **Results:** Twenty-four studies (2810 patients) were included in the analysis. Overall, RT plus EGFR-TKIs had higher ORR (RR = 1.32, 95%CI: 1.13–1.55), DCR (RR = 1.12, 95%CI: 1.04–1.22), and longer OS (HR = 0.72, 95%CI: 0.59–0.89), I-PFS (HR = 0.64, 95%CI: 0.50–0.82) than monotherapy, although with higher overall AEs (20.2% vs 11.8%, RR = 1.34, 95% CI: 1.11–1.62). Furthermore, subgroup analyses found concurrent RT plus EGFR-TKIs could prolong OS (HR = 0.69, 95%CI: 0.55–0.86) and I-PFS (HR = 0.57, 95%CI: 0.44–0.75). Asian ethnicity and lung adenocarcinoma (LAC) patients predicted a more favorable prognosis (HR = 0.69, 95%CI: 0.54–0.88, HR = 0.66, 95% CI: 0.53–0.83, respectively). **Conclusion:** RT plus EGFR-TKIs had higher response rate, longer OS and I-PFS than monotherapy in NSCLC patients with BM. Asian LAC patients with EGFR mutation had a better prognosis with concurrent treatment. The AEs of RT plus EGFR-TKIs were tolerated.

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Introduction

Lung cancer is the leading cause of cancer-related morbidity and mortality worldwide [1]. Approximately 80% of lung cancers were diagnosed non-small cell lung cancer (NSCLC). About 40% of NSCLC patients developed brain metastasis (BM) during the course of diseases, and 10%–25% of advanced NSCLC patients had BM at initial diagnosis, the risk even higher in those with epidermal growth factor receptor (EGFR) mutation [2,3]. The median overall survival (OS) remains disappointing, less than 3 months, for untreated BM patients [4].

Whole-brain radiotherapy (WBRT) has long been a standard therapy for NSCLC with multiple BMs, providing symptom palliation and prolonging survival [5]. Moreover, stereotactic radiosurgery (SRS) has emerged as a principal alternative treatment for oligo-brain metastasis, allowing for precise tumor targeting with minimal invasive [6,7]. Currently, EGFR tyrosine kinase inhibitors (TKIs) have been recognized as the first-line treatment for advanced

NSCLC patients with EGFR mutation-positive [8–10]. Gefitinib and erlotinib can be able to cross the blood–brain barrier (BBB) after disrupted by brain radiotherapy (RT) [11,12]. Particularly, RT and EGFR TKIs might have synergistic anti-tumor effect, with sustained clinical efficacy and favorable safety [13–15]. However, the role of RT combined with EGFR-TKIs for NSCLC patients with BM remains

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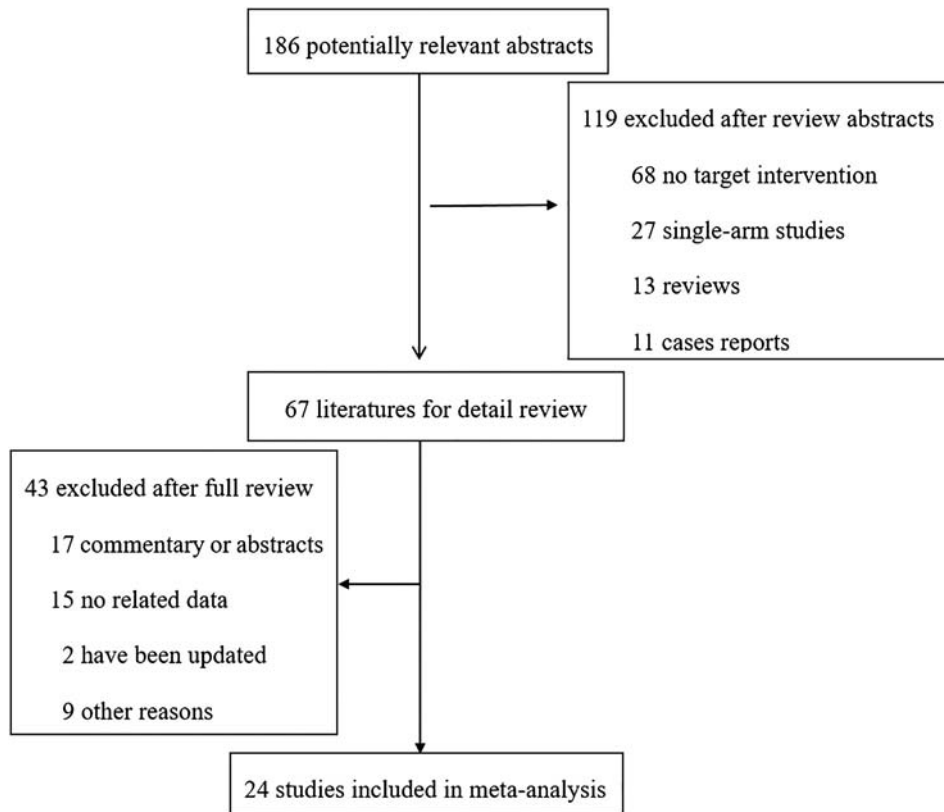


Figure 1. Flow chart of studies included in the meta-analysis.

controversial [16,17]. Therefore, we performed the meta-analysis to comprehensively evaluate the efficacy and safety of RT plus EGFR-TKIs in those patients.

Materials and Methods

Search Strategy and Selection Criteria

Relevant literatures, published between January 1, 2012 and November 28, 2017 from PubMed, EMBASE, Web of Science, Google Scholar, and Cochrane Library were collected, using the terms “lung cancer”, “lung neoplasms”, “lung tumor”, “brain metastasis”, “brain neoplasms”, “radiotherapy”, and “tyrosine kinase inhibitors”.

To be included in the analysis, each study had to fulfill the following criteria: (1) histologically or cytologically confirmed NSCLC and had been diagnosed with one or more BMs by imaging modalities; (2) prospective or retrospective studies; (3) treatment-naïve to the BMs; (4) combination therapy: RT (WBRT, SRS or three-dimensional conformal radiotherapy) combined with EGFR-TKIs; monotherapy: EGFR-TKIs alone or RT ± chemotherapy(CT); (5) only the latest and most complete article was included if duplicate studies were from the same population; (6) full text articles in English or Chinese language were available. Two reviewers independently determined study eligibility, disagreements were resolved by consensus.

Data Extraction

Two investigators conducted independently with the standardized forms according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The following data

were collected from each study: first author, year of publication, source of patients, trial phase, histology, number of patients, median ages, number of female, intervention methods, outcomes and adverse events (AEs). In addition, the result was double-checked by a third reviewer and discrepancies were settled by group discussion.

Methodological Assessment

Two reviewers independently assessed the quality of the included literatures according to The Cochrane Handbook for Systematic Reviews (Version 5.1.0), based on the following criteria: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; (7) other bias. We evaluated methodological quality as low, unclear or high risk of bias. Literatures were defined as low risk of bias (A) when all criteria were assessed as low risk; defined as moderate risk of bias (B) or high risk of bias (C) when one or more criteria were assessed as unclear risk or high risk, respectively.

Definition of Outcomes and Comparisons

The primary outcomes were the OS and I-PFS, then stratified by monotherapy, treatment sequence, ethnicity, histologic type and published year. The effective value of OS and I-PFS were determined by the combination of hazard ratio (HR) and 95% confidence interval (CI), if the CI included 1, then the HR was nonsignificant. For time-to-event data, if a direct report of HR and 95% CI was not possible, estimated value was derived indirectly from other presented data using the methods proposed by Tierney et al. [18].

Table 1. Main characteristics of 24 included studies

First Author	Year	S of Pts	Trial phase	Histology	NP (C/M)	MA (C/M, years)	Female (C/M)	Combination therapy	Treatment sequence	Monotherapy	Outcomes	AEs	SQ
Zhu [21]	2017	CN	Ret	LAC	67/66	56/56	37/35	WBRT/SRS + TKI (gefitinib/erlotinib)	Concurrent	TKI (gefitinib/erlotinib)	OS, I-PFS	N	B
Fan [13]	2017	CN	Ret	LAC	56/41	56/59	34/20	WBRT/SRS + icotinib	Sequential	icotinib	OS, I-PFS, ORR, DCR	N	B
Doherty [22]	2017	CA	Ret	NSCLC	157/27	59/65	111/14	WBRT/SRS+ TKI	Concurrent	TKI	OS, I-PFS, ORR, ORR	N	B
Wang [23]	2016	CN	Ret	NSCLC	37/161	NA	NA	WBRT/SRS + TKI	Sequential	WBRT/SRS + CT	OS, I-PFS, ORR, DCR	Y	B
Jiang [16]	2016	CN	Ret	NSCLC	51/116	NA	26/62	WBRT+TKI (gefitinib/erlotinib/icotinib)	Concurrent	TKI	OS, I-PFS, DCR, ORR	N	B
Chen [24]	2016	CN	Ret	LAC	53/79	52/52	29/52	WBRT+TKI WBRT/SRS + TKI	Concurrent	TKI	OS, I-PFS, ORR OS, DCR, ORR, I-PFS,	N	B
Byeon [25]	2016	KR	Ret	NSCLC	59/62	60/60	36/47	(gefitinib/erlotinib)	Sequential	TKI (gefitinib/erlotinib)	ex-PFS	N	B
Xiang [26]	2015	CN	Ret	NSCLC	39/96	NA	NA	WBRT+TKI	Concurrent	WBRT±CT	OS	N	C
Wang [27]	2015	CN	Pro	NSCLC	37/36	61/62	12/13	3D-RT + gefitinib	Concurrent	3D-RT + VMP	OS, ORR, DCR	Y	B
Liu [28]	2015	CN	Ret	NSCLC	35/15	46.3/47.5	18/8	WBRT+TKI	Concurrent	WBRT	ORR, DCR	N	C
Liu [29]	2015	CN	Ret	LAC	62/34	54/54	NA	WBRT/SRS + TKI	Sequential	TKI ± CT	OS, I-PFS	N	C
Kim [30]	2015	KR	Ret	NSCLC	18/13	55/56	12/10	SRS + TKI	Concurrent	SRS	OS, I-PFS	Y	B
Lee [14]	2014	UK	II	NSCLC	40/40	61.3/62.2	25/29	WBRT+ erlotinib	Concurrent	WBRT+ placebo	OS, I-PFS	Y	A
Cai [31]	2014	CN	Ret	NSCLC	104/178	65/65	42/60	WBRT/SRS + TKI	Concurrent	WBRT/SRS	OS, I-PFS, ex-PFS	N	B
Zhuang [15]	2013	CN	II	LAC	23/31	60/63	13/18	WBRT +erlotinib	Concurrent	WBRT	OS, I-PFS, ex-PFS, ORR, DCR	Y	B
Zhou [32]	2013	CN	Ret	NSCLC	36/22	NA	21/11	WBRT+TKI	Concurrent	WBRT+CT	ORR, DCR	Y	C
Sperduto [17]	2013	MC	III	NSCLC	41/44	61/64	NA	WBRT/SRS + TKI	Concurrent	WBRT/SRS	OS	Y	B
Liu [33]	2013	CN	Pro	NSCLC	52/52	54/51	23/25	WBRT/SRS + TKI	Concurrent	WBRT/SRS	ORR, DCR	Y	B
Fan [34]	2013	CN	Ret	NSCLC	75/135	57/57	32/36	WBRT/SRS + TKI	Concurrent	RT ± CT	OS	N	B
Cai [35]	2013	CN	Pro	NSCLC	65/92	66/66	25/29	WBRT+TKI	Concurrent	WBRT	OS, I-PFS, ORR, DCR	Y	B
Zeng [36]	2012	CN	Ret	NSCLC	45/45	56/52	24/26	WBRT+ gefitinib	Concurrent	gefitinib	OS, I-PFS, ORR, DCR	Y	B
Pesce [37]	2012	SL	II	NSCLC	16/43	57/63	7/16	WBRT+TKI	Concurrent	WBRT+TMZ	OS	Y	B
Wu [38]	2012	CN	Pro	NSCLC	35/18	NA	NA	WBRT+TKI	Concurrent	WBRT	ORR, DCR	N	B
Fu [39]	2012	CN	Ret	NSCLC	38/123	NA	NA	WBRT+TKI	Concurrent	WBRT	ORR, DCR	Y	C

Abbreviations: NP, number of patients; MA, median ages; S of Pts, source of patients; C/M, combination therapy/monotherapy; AEs: adverse events; SQ: study quality; CN, China; KR, Korea; CA, Canada; UK, the United Kingdom; MC, Multicenter; SL, Switzerland; Ret: retrospective; Pro: prospective; NSCLC: non-small cell lung cancer; LAC, lung adenocarcinoma; TKI, tyrosine kinase inhibitor; WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery; 3D-CRT, three-dimensional conformal radiotherapy; TMZ, temozolomide; CT, chemotherapy; OS, overall survival; I-PFS, intracranial progression-free survival; ex-PFS, extracranial progression-free survival; ORR, objective response rate; DCR, disease control rate; N, no mention in the paper; Y, have mentioned in the paper; NA, not available.

Furthermore, objective response rate(ORR), disease control rate (DCR) and AEs were estimated by relative risk (RR). Response rate was calculated using the Response Evaluation Criteria in Solid Tumors. Complete remission: all tumor lesions completely disappeared and normalization of tumor marker level. Partial response: at least a 30% decrease in the sum of the longest diameters (LD) of target lesions. Progressive disease: at least a 20% increase in the smallest sum of the LD of target lesions or the appearance of one or more new lesions. Stabilized disease: neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. AEs were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events.

Statistical analysis

χ^2 and I^2 tests were used to test the statistical heterogeneity of different studies, no heterogeneity was considered when $I^2 < 50\%$ and $P > .1$, then the fixed-effects model was used. Otherwise, the random effects model was applied ($I^2 > 50\%$ and $P < .1$). Z test was used to determine the significance of the pooled HR or RR, and $P < .05$ was considered statistically significant.

Publication bias were assessed by Egger's regression and Begg's funnel plot [19,20], whereas $P < .1$ was set as statistical significance. Sensitivity analysis was performed to determine the influence of each study regarding overall effective size. OS and I-PFS were calculated using effect variables; ORR, DCR and AEs (Grade ≥ 3) were

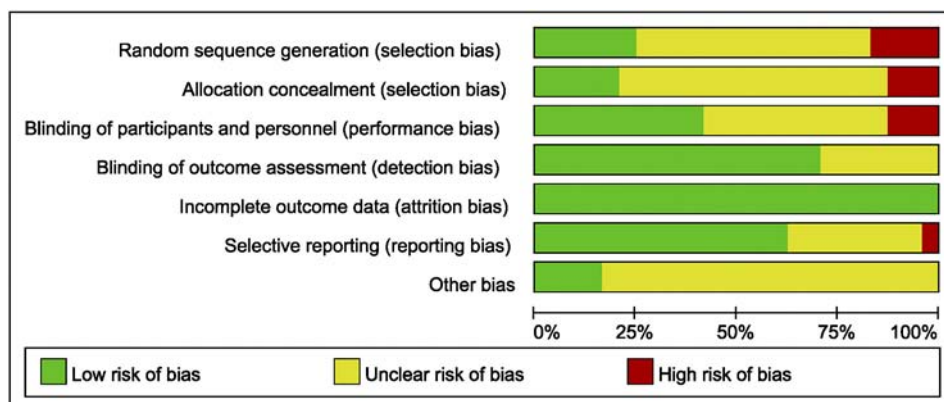


Figure 2. Quality and bias risk assessment of 24 included studies.

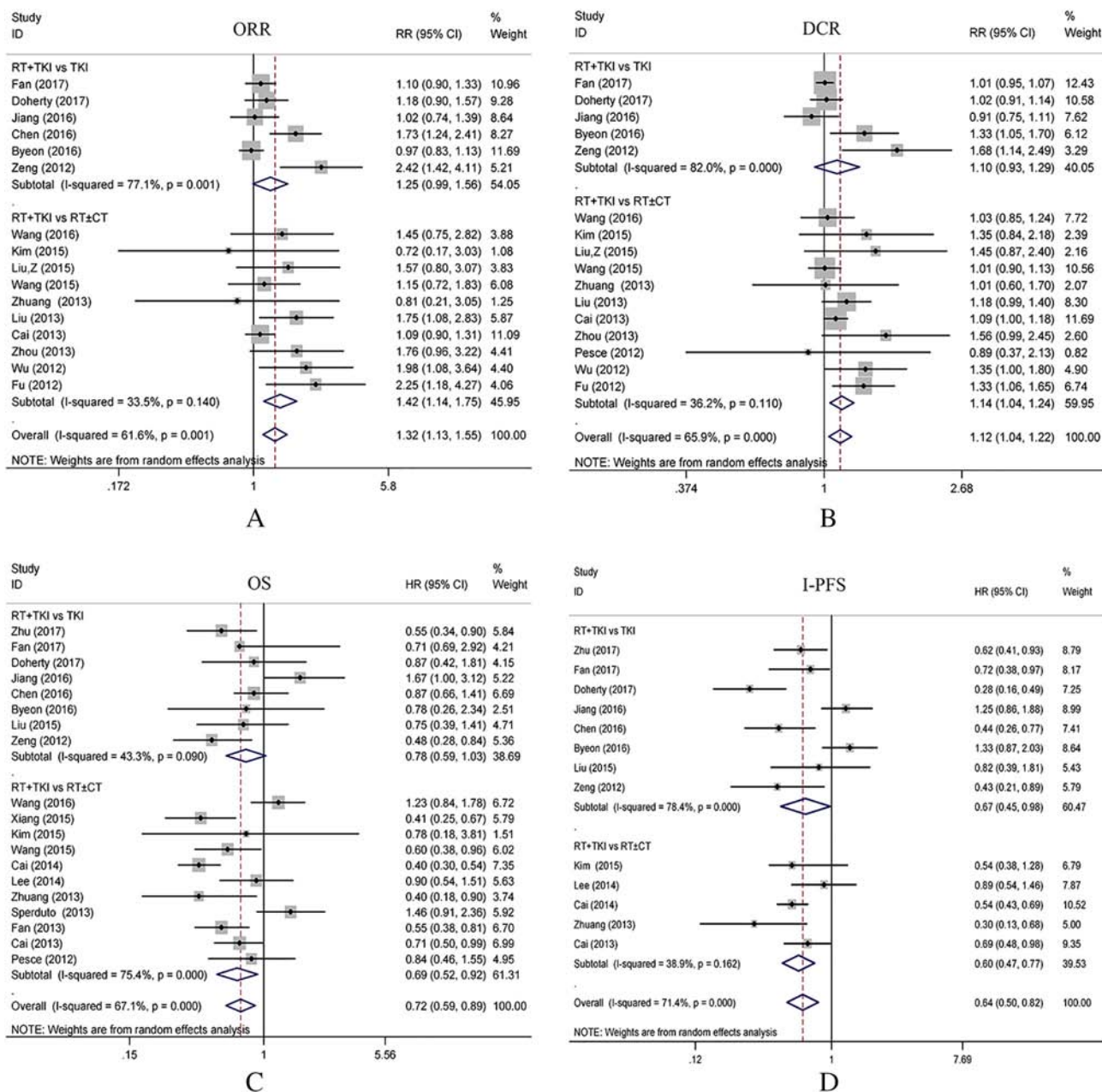


Figure 3. Meta-analysis of RT plus EGFR-TKIs versus monotherapy in NSCLC patients with BM for ORR (A), DCR (B), OS (C), I-PFS (D) and subgroup-analysis of monotherapy. Abbreviations: RT = radiotherapy; EGFR-TKIs = epidermal growth factor receptor tyrosine kinase inhibitors; NSCLC = non-small cell lung cancer; BM = brain metastasis; ORR = objective response rate; DCR = disease control rate; OS = overall survival; I-PFS = intracranial progression-free survival.

analyzed using dichotomous variables. Statistical computations were all performed with STATA Version 12.0 (Stata Corporation LP, College Station, TX). All p values were two sided.

Results

Trial Flow

Literature search process was depicted in Figure 1. We identified 186 potentially relevant abstracts, and then 119 were excluded for the following reasons: 68 no target interventions; 27 single-arm studies; 13 reviews and 11 cases reports. Finally, after carefully reading the

full-text, 24 studies were included in the analysis. The characteristics of these 24 studies were shown in Table 1.

Study Characteristics

Totally, 2810 patients with BM from 24 studies were enrolled in the analysis. RT plus EGFR-TKIs was performed in 1241 (44.2%) patients, while EGFR-TKIs alone in 470 (16.8%) patients, and RT ± CT in 1099 (39%) patients. In addition, 8 prospective studies [14,15,17,27,33,35,37,38] (665 patients, 23.7%) including one phase III [17] and three phase II [14,15,37] clinical trials and 16 retrospective studies (2145 patients, 76.3%) were included. 20 studies (2402 patients, 85.5%) were conducted among Asian while 4 studies [14,17,22,37] (408 patients, 14.5%) among non-Asian and 8

Table 2. HR Value of OS and I-PFS in Subgroups Analyses According to Monotherapy, Treatment Sequence, Ethnicity, Histology and Published Year

	NS	NP	HRs(95%CI)	P	Heterogeneity Test		
					χ^2	I ²	P
OS	19	2384	0.72(0.59,0.89)	0.002	54.79	67.1%	0.000
RT + TKI vs TKI	8	1020	0.78(0.59,1.03)	0.080	12.34	43.3%	0.090
RT + TKI vs RT ± CT	11	1364	0.69(0.52, 0.92)	0.011	40.73	75.4%	0.000
Concurrent	11	1872	0.69(0.55, 0.86)	0.001	44.78	68.7%	0.000
Sequential	4	512	0.99 (0.75, 1.32)	0.959	3.00	0.0%	0.392
Asian	15	1976	0.66(0.53, 0.83)	0.000	42.29	66.9%	0.000
Non-Asian	4	408	1.04 (0.79, 1.38)	0.769	2.95	0.0%	0.399
LAC	5	512	0.69(0.54, 0.88)	0.003	4.10	2.4%	0.393
NSCLC	14	1872	0.75(0.57, 0.97)	0.031	50.69	74.4%	0.000
2015–2017	11	1367	0.78 (0.60, 1.02)	0.071	22.68	55.9%	0.012
2012–2014	8	1017	0.66(0.48, 0.90)	0.009	26.89	74.0%	0.000
I-PFS	13	1624	0.64(0.50, 0.82)	0.000	41.92	71.4%	0.000
RT + TKI vs TKI	8	1020	0.67(0.45, 0.98)	0.040	32.33	78.4%	0.000
RT + TKI vs RT ± CT	5	604	0.60(0.47, 0.77)	0.000	6.55	38.9%	0.162
Concurrent	10	1310	0.57(0.44, 0.75)	0.000	29.32	69.3%	0.001
Sequential	3	314	0.95(0.62, 1.46)	0.822	3.87	48.3%	0.145
Asian	11	1360	0.67(0.45, 0.86)	0.001	31.40	68.2%	0.001
Non-Asian	2	264	0.50 (0.16, 1.56)	0.235	9.17	89.1%	0.002
LAC	5	512	0.58(0.43, 0.76)	0.000	5.14	22.1%	0.274
NSCLC	8	1112	0.68(0.48, 0.96)	0.028	35.47	80.3%	0.000
2015–2017	8	961	0.68(0.47, 0.99)	0.044	31.20	77.6%	0.000
2012–2014	5	663	0.59(0.45, 0.77)	0.000	7.20	44.4%	0.126

Abbreviations: NS, number of studies; NP, number of patients; HRs, hazard ratios; CI, confidence interval.

studies [13,14,16,21,24,25,29,30] (857 patients,30.5%) were performed exclusively in patients with EGFR mutations. As for the intervention methods, 8 studies (1020 patient, 36.3%) were conducted with WBRT/SRS plus TKIs versus TKIs alone [13,16,21,22,24,25,29,36], one study (73 patients, 2.6%) with 3D-CRT plus TKIs/VM-26 (teniposide) [27], the other 15 studies (1717 patients, 61.1%) with WBRT/SRS plus TKIs versus WBRT/SRS ± CT. As far as the treatment sequence, 4 study arms (214 patients, 7.6%) were provided with sequential treatment [13,23,25,29], while 20 study arms (1027 patients, 36.5%) with concurrent treatment. The clinical characteristics of 2810 patients were summarized in Table A1 (Appendix).

Assessment of Study Quality

We evaluated the 24 studies using the seven aspects mentioned above, the risk of bias in this analysis were shown in Figure 2, while the details in Figure S1. Four studies were with random allocation [14,17,27,37], while two with the methods discussion [17,37]. One study concealed the allocation and blinding method [15]. All of the articles applied the intention-to-treat analysis. Finally, 1/24 studies received quality scores of A, while 18/24 of B and 5/24 of C, as shown in Table 1.

Meta-Analysis of Objective Response Rate and Disease Control Rate

ORR and DCR were assessed respectively in 16 studies [13,15,16,22–25,27,28,30,32,33,35–39]. The overall ORR was 64.0% (13.0%–85.7%) in combination therapy and 40.5% (14.4–78.0%) in monotherapy; the overall DCR was 82.7% (27.9%–98.2%) in combination therapy and 71.9% (31.3–97.6%) in monotherapy. Random effects models were used to pool the RR in both ORR and DCR due to the statistical heterogeneity (I² = 61.6%, P = .001; I² = 65.9%, P = .000, respectively). As a result, combination therapy resulted in higher ORR (RR = 1.32, 95%CI: 1.13–1.55, P = .000) and DCR (RR = 1.12, 95%CI: 1.04–1.22,

P = .005) than monotherapy. However, subgroup analysis of combination therapy versus TKIs alone showed no improvement in both ORR (RR = 1.25, 95%CI: 0.99–1.56, P = .057, Figure 3A) and DCR (RR = 1.10, 95%CI: 0.93–1.29, P = .254, Figure 3B) in NSCLC patients with BM.

Meta-Analysis of Overall Survival and Intracranial progression-free survival

The OS was evaluated in 19 studies (2384 patients, 85%) [13–17,21–27,29–31,34–37], and I-PFS was in 13 studies (1570 patients, 56%) [13–16,21,22,24,25,29–31,35,36] including the extracranial progression-free survival (ex-PFS) in three (457 patients, 16%) of them [15,25,31]. Random effects models were used to pool the HR in both OS and I-PFS based on the heterogeneity values (I² = 67.1%, P = .000; I² = 75.5%, P = .017, respectively). As a result, combination therapy resulted in longer OS (HR = 0.72, 95% CI: 0.59–0.89, P = .002, Figure S2 A) and I-PFS (HR =0.64, 95% CI: 0.50–0.82, P = .000) than monotherapy, except for ex-PFS (HR = 0.64, 95%CI: 0.35–1.15, P = .133)(Figure S2 B). However, the subgroup analysis of combination therapy versus TKIs alone showed no improvement in OS (HR = 0.78, 95%CI: 0.59–1.03, P = .08, Figure 3C), although prolonged I-PFS (HR = 0.67, 95% CI: 0.45–0.98, P = .04, Figure 3D) was found in NSCLC patients with BM. Moreover, when the analysis was limited to EGFR mutations, no improvement was found in combination therapy for OS (HR 0.85, 95%CI: 0.66–1.08, P = .125, Figure S3 A) and I-PFS (HR 0.79, 95% CI: 0.60–1.05, P = .100, Figure S3 B), regardless of concurrent vs. sequential treatment, RT plus TKI vs. TKI alone/RT ± CT.

We also conducted multiple subgroup analyses, shown in Table 2. As for concurrent versus sequential treatment, we found that concurrent RT plus EGFR-TKIs could significantly prolong OS (HR = 0.69, 95% CI: 0.55–0.86, P = .001) and I-PFS (HR = 0.57, 95%CI: 0.44–0.75, P = .000) in NSCLC patients with BM. Moreover, sequential treatment could not improve both of them (HR = 0.99, 95% CI:0.75–1.32, P = .959; HR = 0.95, 95% CI: 0.62–1.46, P = .822, respectively) (Figure 4, A and B). Furthermore, better OS (HR = 0.66, 95%CI: 0.53–0.83, P = .000, Figure 4C) and I-PFS (HR = 0.67, 95% CI: 0.52–0.86, P = .001, Figure 4D) were found in Asian NSCLC patients with BM. Lung adenocarcinoma (LAC) patients with BM had favorable prognosis, with HR 0.69 (95%CI: 0.54–0.88, P = .003, Figure 4E) and 0.58 (95%CI: 0.43–0.76, P = .000, Figure 4F) for OS and I-PFS respectively. Recent published year (2015–2017) showed no improvement in OS (HR = 0.78, 95%CI: 0.60–1.02, P = .071, Figure S4 A), although prolonged I-PFS was found (HR = 0.68, 95% CI: 0.47–0.99, P = .000) (Figure S4 B).

As for prognostic factors from included patients, symptomatic brain metastases (P = .003), No of BMs >3 (P = .000), extracranial metastases (P = .000), brainstem metastases (P = .000), KPS <70 (P = .000), ECOG PS >1 (P = .000) were poor prognostic factors. However, female (P = .000), age< 65 years old (P = .000), never smoking (P = .000), EGFR exon 19 deletion (P = .001) were good prognostic factors (Figure S5).

Adverse Events

The AEs were analyzed in 12 studies (1150 patients, 40.9%) [14,15,17,23,27,30,32,33,35–37,39]. The overall incidence rate of AEs was higher in the combination therapy than monotherapy (20.2% vs 11.8%, RR = 1.34, 95% CI: 1.11–1.62; P = .003) with random effects models due to the heterogeneity (P = .000, I² = 45.0%).

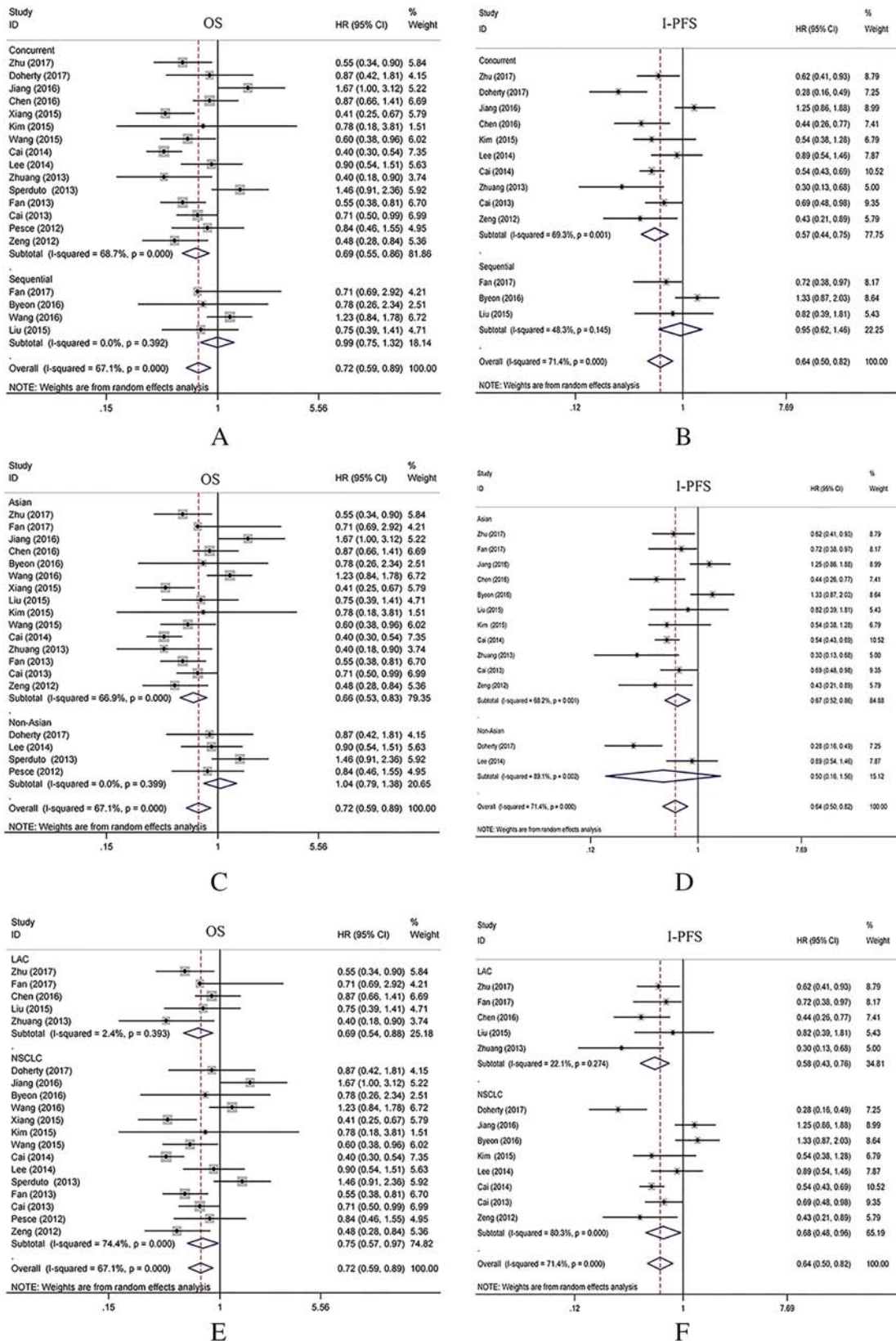


Figure 4. Subgroup analysis of OS and I-PFS in concurrent and sequential treatment (A and B), Asian and non-Asian (C and D), LAC and NSCLC (E and F), respectively. Abbreviations: OS = overall survival; I-PFS = intracranial progression-free survival; LAC = Lung adenocarcinoma; NSCLC = non-small cell lung cancer.

Table 3. Stratified Analysis of the Reported Overall Adverse Events in the 12 Included Studies

Adverse event	NS	NP	Incidence rate(%)		RRs (95%CI)	P	Heterogeneity test		
			Treatment group	Control group			χ^2	I ²	P
headache	6	470	22(0–35.4)	21.4(10–31.8)	1.13(0.81,1.58)	0.469	4.79	0.0%	0.481
fatigue	5	576	20.5(0–44.2)	12.7(1.9–46.5)	1.07(0.74,1.50)	0.721	1.95	0.0%	0.744
dizziness	3	242	25.5(5.6–47.8)	19.1(0–21.7)	1.51(0.80,2.83)	0.200	2.70	26.0%	0.259
rash	8	763	42.2(20–44.4)	6.7(0–44.4)	6.71(1.62,27.86)	0.009	55.84	87.5%	0.000
dry skin	2	134	15.9(2.5–39.1)	1.4(0–3.3)	8.16(1.51,4.17)	0.015	0.54	0.0%	0.462
mucositis	2	113	5.1(4.3–6.3)	1.4(0–3.2)	2.85(0.36, 2.29)	0.319	0.68	0.0%	0.409
nausea & vomiting	8	903	26(0–51.9)	17.3(0–48.1)	1.14(0.90, 1.40)	0.266	4.65	0.0%	0.703
anorexia	2	134	19(5–43.5)	15.5(7.5–25.8)	1.58 (0.50, 4.5)	0.397	1.61	37.7%	0.205
diarrhea	8	816	19.6(5–42.2)	7.8(0–37.8)	2.16 (1.13, 4.15)	0.020	12.27	42.9%	0.092
constipation	2	134	17.5(2.5–17.5)	11.3(0–25.8)	1.74 (0.83, 3.63)	0.141	0.12	0.0%	0.725
pneumonitis	3	327	9.3(0–30.4)	4.9(0–22.6)	1.78 (0.32, 9.92)	0.510	3.72	46.3%	0.155
dyspnea	2	139	28.6(12.5–35)	18.1(0–37.5)	2.32(0.19,28.83)	0.512	3.03	67.0%	0.082
leucopenia/neutropenia	5	541	13.6(0–28.9)	16.8(8.7–25)	0.90 (0.50, 1.61)	0.722	5.75	30.5%	0.218
anemia	5	562	7.4(0–15.2)	7.3(5–10.9)	0.93 (0.35, 2.49)	0.889	6.19	35.3%	0.186
thrombocytopenia	3	325	5.2(0–8.7)	9.3(6.5–14.7)	0.70 (0.19, 2.5)	0.586	3.04	34.2%	0.219
myelosuppression	2	219	18.7(0–27.8)	8.2(6.5–9.1)	0.29 (0.08, 1.07)	0.064	2.32	56.8%	0.128
transaminases	3	171	3.4(0–5)	9.4(7.7–10)	2.15 (0.75, 6.17)	0.155	2.17	7.8%	0.338
myopathy	2	111	8.1(5.3–11)	11.9(8.3–31.8)	0.43 (0.10, 1.83)	0.253	0.16	0.0%	0.693
overall	12	1150	20.2(0–51.9)	11.8(0–46.5)	1.34 (1.10,1.62)	0.003	127.26	45.0%	0.000

Abbreviations: NS, number of studies; NP, number of patients; RRs, risk rates; CI, confidence interval.

The most common AEs in combination therapy versus monotherapy were rash (42.2% vs 6.7%, RR = 6.72, 95%CI: 1.62–27.86; *P* = .009), dry skin (15.9% vs 1.4%, RR = 8.16, 95%CI: 1.51–44.17; *P* = .015) and diarrhea (19.6% vs 7.8%, RR = 2.17, 95%CI: 1.13–4.15; *P* = .020), as shown in Table 3 and Figure S6.

Test of Heterogeneity and Sensitivity Analysis

The heterogeneity was found with the systemic analysis of OS (I² = 67.1%, χ^2 = 54.79, *P* = .000) and I-PFS (I² = 74.1%, χ^2 = 41.92, *P* = .000). More importantly, no heterogeneity was detected in the subgroup analysis of non-Asian and sequential treatment for OS. The statistical heterogeneity was reduced after the subgroup analyses for OS (RT + TKI vs TKI, Asian, LAC, published year 2015–2017) and I-PFS (RT + TKI vs RT ± CT, Asian, sequential treatment and published year 2012–2014) (Table 2). Therefore, the most important sources of heterogeneity were different ethnicity, treatment sequence and histologic types.

Furthermore, the results of sensitivity analysis regarding OS and I-PFS were relatively stable, and excluded each of the study did not influence the overall effective size. Thus, there were no potential and important bias factors associated with interventions (Figure S7).

Publication Bias

The Begg’s funnel plot and Egger’s regression test were applied for detecting publication bias in the meta-analysis. No funnel plot asymmetry was found for OS and I-PFS (Begg’s test, *P* = .944, *P* = .428; Egger’s test, *P* = .474, *P* = .631, respectively). Therefore, there was no evidence of significant publication bias in the analysis (Figure S8).

Discussion

BM is a common complication of lung cancer and associated with poor outcomes. Patients with driver mutations may have a higher incidence of BM due to the prolonged survival with targeting agents [40,41]. RT, including WBRT and SRS, has long been recognized as a standard therapy in NSCLC patients with BM, even when the patients have asymptomatic or single-brain metastasis [42–44].

Moreover, EGFR-TKIs such as gefitinib and erlotinib, which have the possibility of crossing the BBB and competing with adenosine triphosphate, could enhance radiosensitization [45,46]. Hence, RT combined with EGFR-TKIs seems to be promising strategy for NSCLC patients with BM.

Previously, one meta-analysis [47] enrolled only eight publications, and another update [48] had issues involved in 1/15 studies. Therefore, we comprehensive analysis of 24 studies with different monotherapy, treatment sequence, ethnicity, histologic type and published year for both OS and I-PFS. Besides, the stratified analyses for overall AEs were also been performed. As a result, we present more precise update information about the efficacy and safety of RT plus EGFR-TKIs in NSCLC patients with BM.

This meta-analysis showed that combination therapy produced higher ORR and DCR, with longer OS and I-PFS than monotherapy in NSCLC patients with BM. The common AEs of EGFR-TKIs which were tolerated, were rash, dry skin and diarrhea. As for subgroup analyses, we found that combination therapy versus TKIs alone showed no improvement in OS, ORR and DCR, although prolonged I-PFS was found. Thus, the increased efficacy of combination therapy was interpreted cautiously by the TKI therapy. Furthermore, concurrent RT plus EGFR-TKIs could prolong the OS and I-PFS while sequential treatment had no improvement. Then, it confirmed the synergistic effect of RT and EGFR-TKIs [3,31,46]. Additionally, a larger retrospective study had demonstrated that upfront RT, especially SRS, and followed by EGFR-TKIs could prolong OS in NSCLC patients with EGFR mutation and BM [49]. However, it needs to be confirmed by prospective studies. Likewise, Asian LAC patients with BM had an improvement for both OS and I-PFS, which may be ascribed to TKIs. As is known, Asian NSCLC patients had a higher EGFR mutation rate than other ethnicities, with 60% and 10%–15%, respectively [50,51]. However, the discordant EGFR mutation rate between primary (0%) and brain metastatic tumors (32%) was found [52,53]. Therefore, molecular mechanisms need to be studied with EGFR-TKIs in the process of BM.

Certain limitations must be mentioned in the meta-analysis. Firstly, the 24 included studies did not have high methodological quality. Then, multiple subgroup analyses were performed to increase the reliability of

our results. Secondly, several important information such as number of BMs, performance status, EGFR mutation, and extracranial disease control were not consistently reported. But no significant difference was found in each of the included studies. Thirdly, heterogeneity was found in this meta-analysis. Multiple subgroup analyses indicated that different ethnicity, treatment sequence and histologic types may be the major sources of heterogeneity. Last but not least, although the publication bias were not found in this analysis, English and Chinese articles only could not completely avoid language bias.

Conclusion

Our comprehensive analysis suggested that RT plus EGFR-TKIs resulted in higher response rate, with longer OS and I-PFS than monotherapy in NSCLC patients with BM. Asian LAC patients with EGFR mutation will have a better prognosis with concurrent treatment. The common AEs of EGFR-TKIs were rash, dry skin and diarrhea. Nonetheless, more high quality and large-scale clinical trials are necessary to confirm the efficacy and safety of RT plus EGFR-TKIs in NSCLC patients with BM.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tranon.2018.07.003>.

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Disclosures

The authors report no conflicts of interest in this work.

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