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TOPIC REVIEW

Combined treatment for non-small cell lung cancer and breast cancer patients with brain metastases with whole brain radiotherapy and temozolomide: a systematic review and meta-analysis

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Abstract Brain metastasis is the leading cause of death among advanced non-small cell lung cancer (NSCLC) and breast cancer patients. The standard treatment for brain metastases is radiotherapy. The combination of radiotherapy and chemotherapy has been tested. However, the management of brain metastases has yet to be successful. Here, we aimed to determine the efficacy and safety of whole brain radiotherapy (WBRT) alone or in combination with temozolomide (TMZ) in NSCLC and breast cancer patients with brain metastases. A systematic review of PubMed, CNKI (China National Knowledge Infrastructure) and WANFANG (WANGFANG data) involving 870 patients were conducted. Fourteen randomized controlled trials (RCTs) were independently identified by two reviewers. The primary outcome measures were objective response rate (ORR), overall survival (OS), progression-free survival (PFS) and toxicity. The ORR was better with combination therapy of WBRT and TMZ than with WBRT alone (RR = 1.34, $p < 0.00001$) and subgroup analysis showed a significantly superior ORR in NSCLC patients (RR = 1.38, $p < 0.00001$), but not in breast cancer patients (RR = 1.03, $p = 0.86$). OS and PFS did not significantly differ between combination therapy and WBRT alone. A higher rate of toxicity was observed in combination therapy than in WBRT alone (RR = 1.83, $p = 0.0006$). No advantages of concurrent WBRT and TMZ were observed in breast cancer patients with brain metastases. Combination therapy was associated with improved ORR in NSCLC patients, especially in Chinese patients. As a "surrogate endpoint" for OS, ORR may allow a conclusion to be made about the management of NSCLC with brain metastases with the combination of WBRT and TMZ. However, it needs to be validated to show that improved ORR predicts the treatment effects on the clinical benefit. The ORR may be valid for a particular indication such as status of MGMT promoter methylation.

Keywords Whole brain radiotherapy · Temozolomide · Non small cell lung cancer · Breast cancer · Brain metastases

Introduction

Brain metastasis (BM) is the leading cause of death among lung cancer and breast cancer patients, accounting for approximately 30–40 and 15–25% of lung cancer and breast cancer cases, respectively [1, 2]. Whole brain radiotherapy (WBRT) has been considered one of the standard treatments for patients with BM, resulting in a median survival of 10 months and a 5-year survival of only 5% [3, 4]. New standards of treatment including tyrosine kinase inhibitor (TKI) and combination therapies are being adopted. For limited resectable brain metastases, resection followed by WBRT is recommended. The combination of chemotherapy and radiotherapy has been

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reported to improve the 5-year survival to 10–15% in stage III NSCLC [5]. Over the past decade, concomitant chemotherapy and radiotherapy has become the established treatment for patients with stage III NSCLC [6]. However, a majority of patients suffer from chemotherapy-induced toxicity, especially elderly patients. Temozolomide (TMZ) is an oral alkylating agent that can cross the blood–brain barrier, causing DNA damage and inducing death in cancer cells. TMZ is usually used as a second-line treatment for astrocytoma and a first-line treatment for glioblastoma multiforme. The addition of temozolomide to radiotherapy for patients with glioblastoma has been shown to result in statistically significant benefit in survival [7]. Although combination of radiotherapy and temozolomide has been clinically used for patients with multiple brain metastatic lesions, the outcomes are still generally poor, and clinical practice guidelines are not routinely followed.

This study aimed to assess the objective response rate (ORR), overall survival (OS) and progression-free survival (PFS) in NSCLC and breast cancer patients with brain metastases by performing a systematic review of randomized controlled trials in the literature. Incremental benefit of combination of WBRT and TMZ over WBRT alone was described in NSCLC patients with brain metastases, but not in breast cancer patients with brain metastases.

Materials and methods

Search strategy

We performed a search of PubMed, CNKI (China National Knowledge Infrastructure) and WANFANG (WANGFANG data) from their inception to October 2016 using a combination of keywords and search strategies with Medical Subject Headings (MeSH) ("Lung Neoplasms"[Mesh] OR "Breast Neoplasms"[Mesh]) AND ("brain metastasis" OR "intracranial metastases" OR "brain neoplasms" OR "brain metastases" OR "intracranial metastatic tumor") AND ("radiotherapy" OR "radiation therapy") AND (temozolomide OR "TMZ" OR "methazolastone" OR "M and B 39831" OR "M and B-39831" OR "Temodar" OR "Temodal" OR "TMZ-Bioshuttle" OR "CCRG 81045" OR "CCRG-81045" OR "NSC 362856" OR "NSC-362856") AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [title + abstract] OR placebo [title + abstract] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh]). We also performed a search of CNKI and WANFANG database with the same keywords in Chinese.

Study selection

All articles that met the following criteria were eligible: (1) parallel randomized controlled trials (RCT) with voluntarily enrolled patients; (2) patients diagnosed with NSCLC or breast cancer with brain metastases; and (3) trials enrolling patients with a World Health Organization (WHO) performance score of ≤ 2 or ECOG performance status ≤ 2 or Karnofsky performance status [KPS] of ≥ 50. The study arms were classified as the combination of WBRT and temozolomide or WBRT alone. The outcomes in terms of ORR (ORR = complete remission + partial remission), median OS, PFS, and adverse effects were extracted.

Screening and data extraction

Standardized data forms and data extraction training exercises were developed to achieve a high level of consensus between reviewers [8, 9]. To determine if a study citation met the inclusion criteria, the titles and abstracts were screened independently by two methodologically trained reviewers (JR. T. and YE. L.). These reviewers independently assessed the full text of articles to confirm the eligibility of the articles. Any disagreement was resolved by discussion. All the studies included contained the following data: first author's last name, year of publication, sample size, percentage of men, average ages of patients, number of metastases, histology, primary objective, interventions and outcomes (Table 1).

Assessment of methodology quality

The internal validity of trials was assessed by using the Cochrane collaboration's tool, which evaluates the risk of bias arising from each of the six domains: (1) details of the randomization method; (2) allocation concealment; (3) blinding of participants and personnel; (4) incomplete outcome data; (5) selective outcome reporting; and (6) other sources of bias. Each of the six items was scored as "low risk", "unclear risk", or "high risk" (Fig. 1a, b).

Statistical analysis

The risk of bias and internal validity of trials were assessed by Cochrane RevMan 5.3 software. All statistical analyses were performed with STATA version 14.0 and R. All statistical tests were 2-sided. Risk ratio (RR) or hazard ratio (HR) [10] and its 95% confidence interval (CI) was used to quantify the effect of the treatment on ORR and toxicity as well as overall survival and PFS. When using the RR for evaluation, the significance was assessed using the Mantel–Haenszel test. In addition, inverse variance test was adopted when the HR was estimated. Q tests and I^2 tests

Table 1 Summary of the characteristics of patients and treatment in the included trials

Trial	Sample size (T/C)	Male (T/C, %)	Age (T/C) (years)	BM	WBRT usage	TMZ usage	Histology (T/C)		Outcomes	Primary objective
							NSCLC	BC		
Cao [12]	50/50	0/0	58 (38–79)/54 (29–78)	≥1	30 Gy/10 f/2 w	During WBRT 75 mg/m^2/d After WBRT 75 mg/m^2/d 5 days every 28 days	0	50/50	ORR, PFS, OS, neurologic symptoms, tolerability	ORR
Gamboa-Vignolle [13]	28/27	11/19	50 (20–74)/54 (28–73)	≥1	30 Gy/10 f/2 w	1 h before each WBRT, at a fixed dose of 200 mg on Mondays, Wednesdays and Fridays and at a fixed dose of 300 mg on Tuesdays and Thursdays	20/14	8/13	ORR, PFS, toxicity, OS	ORR
Chua [14]	47/48	64/67	59 (38–78)/62 (43–79)	≥1	30 Gy/10 f/2 w	During WBRT 75 mg/m^2/d After WBRT 75 mg/m^2/d 5 days every 28 days	47/48	0	MST, central nervous system progression, Toxicity, Adverse event	OS
Gu [15]	52/50	54/46	60/59	≥1	40 Gy/20 f/4 w	200 mg/m^2/d 5 days every 28 days for four cycles	52/50	0	QoL, ORR, toxicity, 1 year survival rate, MST	
Hassler [16]	22/13	59/62	69 (36–85)/64 (54–78)	≥1	30 Gy/10 f/2 w or 40 Gy/20 f/4 w	During WBRT 75 mg/m^2/d 2 weeks after WBRT 100 mg/m^2/d 2 weeks on/2 weeks off for up to 6 months	22/13	0	ORR, MST, Toxicity, Adverse events, PFS	Safety and toxicity
Liu [17]	21/16	54	(43–71)	≥1	40 Gy/20 f/4 w	250 mg/m^2/d 5 days every 28 days for three cycles	21/16	0	QoL, ORR, toxicity, MST	
Mu [18]	29/29	62/59	61 (52–74)/61 (51–75)		400 cGy/20 f/1 m	150 mg/m^2/d 5 days every 28 days for four cycles	29/29	0	ORR, MST, 1 year survival rate	
Sun [19]	30/30	57/53	59/59	≥1	40 Gy/20 f/4 w	During WBRT 75 mg/m^2/d 4 weeks	30/30	0	ORR, MST, toxicity	
Xie [20]	25/25	72	56 (30–70)	≥1	40 Gy/200 cGy/20 f/4 w	200 mg/m^2/d 5 days every 28 days	25/25	0	ORR, MST, toxicity	

Table 1 (continued)

Trial	Sample size (T/C)	Male (T/C, %)	Age (T/C) (years)	BM	WBRT usage	TMZ usage	Histology (T/C)		Outcomes	Primary objective
							NSCLC	BC		
Xu [21]	40/40	60	54		40 Gy/20 f/4 w	During WBRT 75 mg/m^2/d 4 weeks after WBRT 150 mg/m^2/d (after the first cycle if drug was well tolerated, can adjusted to 200 mg/m^2) 5 days every 28 for up to six cycles	40/40	0	ORR, OS, PFS, toxicity, QoL	
Yang [22]	23/23	54	46 (37–70)		80 Gy/4 Gy/20 f/1 m	200 mg/m^2/d 5 days every 28 days for two to six cycles	23/23	0	ORR, toxicity	
Zhao [25]	25/25	0/0	50 (33–62)	≥1	36–40 Gy/1.8–2.0 Gy/20 f	After the 5th day of WBRT 100 mg/m^2/d 5 days every 28 days	0	25/25	ORR, 1 year survival rate, toxicity	
Zhao [23]	30/30	53/57	58 (38–69)/58 (36–68)		40 Gy/20 f	During WBRT 75 mg/m^2/d 4 weeks after WBRT 150 mg/m^2/d (after the first cycle if drug was well tolerated, can adjusted to 200 mg/m^2) 5 days every 28 for up to six cycles	30/30	0	ORR, medial time to recurrence, MST, toxicity, QoL	
Zhou [24]	20/22	70/68	61/65	≥1	40 Gy/20 f/4 w	During WBRT 75 mg/m^2/d 4 weeks after WBRT (first cycle: 150 mg mg/m^2/d; second to the sixth cycles: 200 mg/m^2/d) for 5 days every 28 days	20/22	0	ORR, toxicity, OS	

T therapeutic group, *C* control group, *BM* brain metastases, *Gy* Gray, *f* fraction, *w* week, *m* month, *d* day, *NSCLC* non-small lung cancer, *BC* breast cancer, *WBRT* whole brain radiation therapy, *TMZ* temozolomide, *PFS* progression-free survival, *ORR* objective response rate, *MST* medial survival time, *QoL* quality of life, *OS* overall survival

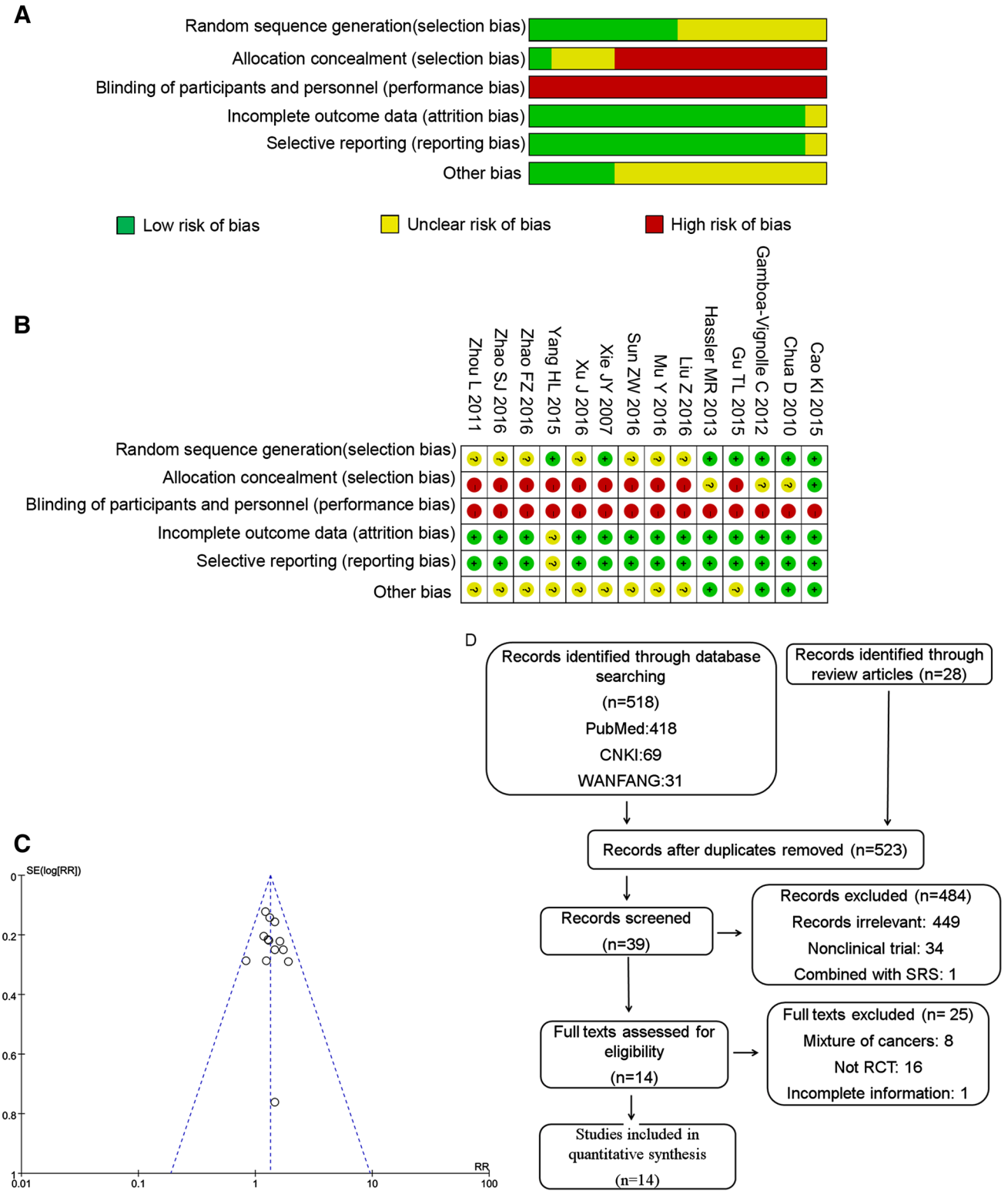


Fig. 1 Study selection, screening and data extraction. **a** Overall assessment of the risk of bias. Using the Cochrane Risk of Bias Tool, selection bias was assessed by random sequence generation and allocation concealment; performance bias, by blinding of participants and personnel; attrition bias, by incomplete outcome data; reporting bias, by selective reporting; and other bias, by other sources of bias. **b** The risk of bias assessment for each included study. Using the Cochrane Risk of Bias Tool, the risk of bias for each publication was summarized. "+/*green*" = Yes; "−/*red*" = No; "?/*yellow*" = unclear; **c** Funnel plot of the 13 RCTs with objective response data (ORR). **d** Flowchart of the trial selection process

were adopted to estimate heterogeneity. When $p < 0.05$ and $I^2 > 50\%$, the heterogeneity was considered statistically significant and a random-effects statistical model was applied. Otherwise, the heterogeneity was considered not statistically significant and a fixed-effect model was applied [11]. Publication bias was evaluated with funnel plot and Egger regression asymmetry test (Fig. 1c).

Results

Five hundred and twenty-three relevant publications were searched, and 14 studies were finally identified. Of the RCTs included in the systematic review, 11 trials enrolled NSCLC patients, two trials enrolled breast cancer patients and one enrolled both [12–25]. The selection process and reasons for exclusion are detailed in Fig. 1d. The included studies with 870 patients from 14 RCT were published between 2007 and 2016, and among them, 585 patients were from ten Chinese studies [15, 17–25]. There were 699 patients with NSCLC, and among them, 359 received combination therapy with WBRT and TMZ, and 340 patients received WBRT alone. Eighty-three out of 171 patients with breast cancer received combination therapy, and 88 received WBRT alone (Table 1; Fig. 1d). Assessment of publication bias showed a lack of bias.

Objective response rate

The objective response rate (ORR) was superior in patients receiving combination WBRT and TMZ compared to those receiving WBRT alone (RR = 1.34, 95% CI 1.19–1.50, $p < 0.00001$, Fig. 2a). A subgroup analysis of RCTs in Chinese or non-Chinese patients showed significantly superior ORRs in Chinese patients than in non-Chinese patients (Chinese: RR = 1.37, 95% CI 1.21–1.55, $p < 0.00001$; non-Chinese: RR = 1.19, 95% CI 0.85–1.68, $p = 0.31$, Fig. 2a, 1.1.1; 1.1.2). Of the RCTs in NSCLC patients, the ORR was significantly superior for combination therapy than for WBRT alone (RR = 1.38, 95% CI 1.21–1.57, and $p < 0.00001$, Fig. 2b, 1.1.1). However, our study showed no advantage in terms of ORR for combination therapy in breast cancer patients (RR = 1.03, 95% CI 0.73–1.47, and $p = 0.86$, Fig. 2b, 1.1.2), indicating that breast cancer patients with brain metastases were less likely to benefit from combination WBRT and TMZ.

Safety outcomes

Treatment-related deaths was observed among patients with combination therapy (1/315) but not in those with WBRT alone (0/299). Grade II or more toxicity was more frequent in patients receiving combination therapy (100/315) versus in patients receiving WBRT alone (45/299). The rate of treatment-related toxicity of combination therapy was 1.83 times that of WBRT alone (RR = 1.83, 95% CI 1.30–2.59, and $p = 0.0006$, Fig. 3a). Of the RCTs in only NSCLC patients or only breast cancer patients, the rate of toxicity of combination therapy was significantly higher than that of WBRT alone (RR = 2.27, 95% CI 1.17–4.40, and $p = 0.02$ and RR = 1.65 95% CI 1.10–2.45, and $p = 0.01$, respectively, Fig. 3b 1.1.1, 1.1.2). When considering haematological toxicity, the incidence of hematological toxicity in combination therapy was 67/315 versus 33/299 for WBRT alone (RR = 1.85, 95% CI 1.31–2.61, and $p = 0.0005$, Fig. 3b 1.1.3). The non-hematological toxicity displayed no significant difference between the two groups (RR = 1.19, 95% CI 0.38–3.79, $p = 0.77$, Fig. 3b 1.1.4).

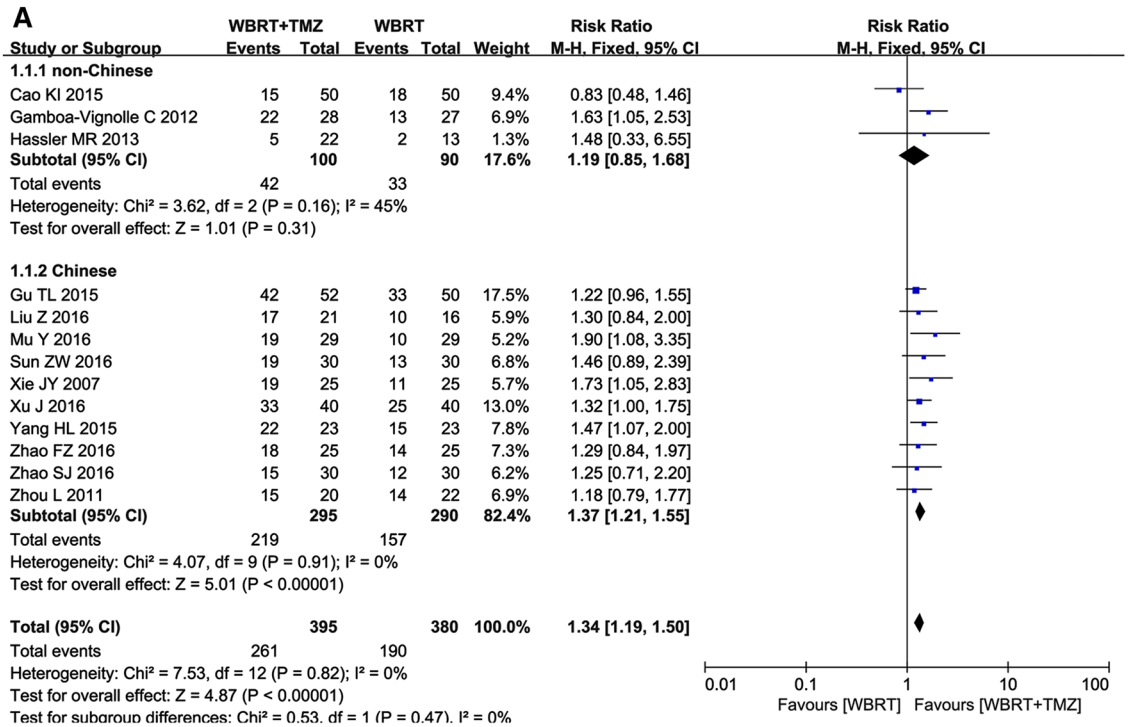
Survival

There was variation in overall survival in the RCTs. Although OS was better with combination therapy, the difference was not significant (HR = 0.61, 95% CI 0.36–1.03, and $p = 0.07$, Fig. 4a). Subgroup analyses also did not show differences in NSCLC patients or breast cancer patients (HR = 0.64, 95% CI 0.30–1.36, and $p = 0.25$; HR = 0.56, 95% CI 0.22–1.48, and $p = 0.24$, respectively, Fig. 4b 1.1.1, 1.1.2). There was no significant difference in PFS between the different treatment groups (HR = 0.85, 95% CI 0.55–1.30, and $p = 0.45$, Fig. 4c).

Discussion

In this study, the addition of TMZ to WBRT demonstrated a better ORR in the treatment of NSCLC patients with brain metastasis. However, the combination therapy displayed modest benefit for breast cancer patients with brain metastasis. The benefits are dependent on the primary site of cancer and are limited to improvement in ORR. Although a trend towards better OS was seen with combination therapy in NSCLC patients with brain metastasis, the effect was not significant.

OS has been the gold standard for clinical trial endpoints in oncology. This endpoint may be confounded by other factors such as subsequent therapies and requires a longer time to follow up with patents [26]. Given the number of potential advances in current combination therapies, phase III trial endpoints can take years to complete, which is inadequate [6]. Over the years, surrogate endpoints such as objective response rate and progression-free survival have been employed and are usually beneficial in evaluating therapies. Response rates can be accurately assessed and evaluated by determining tumor progression. Because spontaneous remission is rare, ORR provides



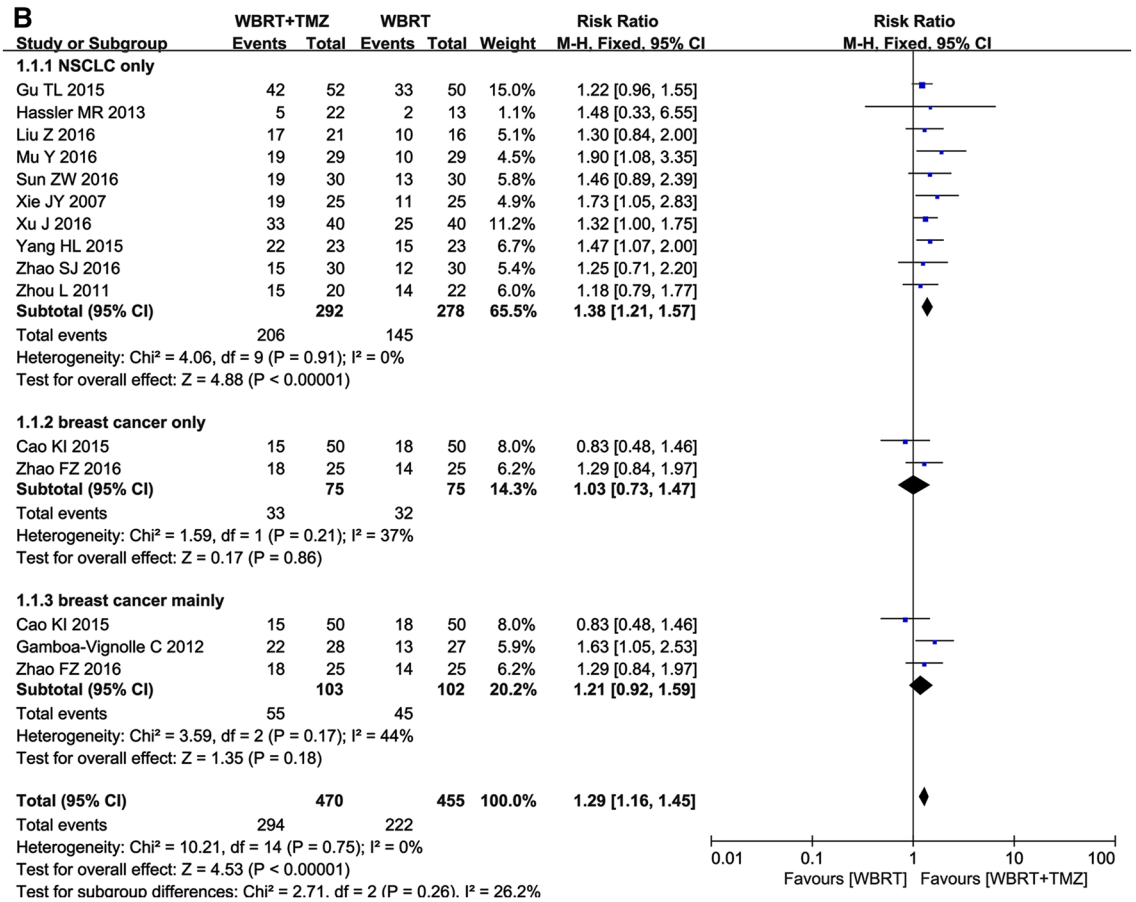
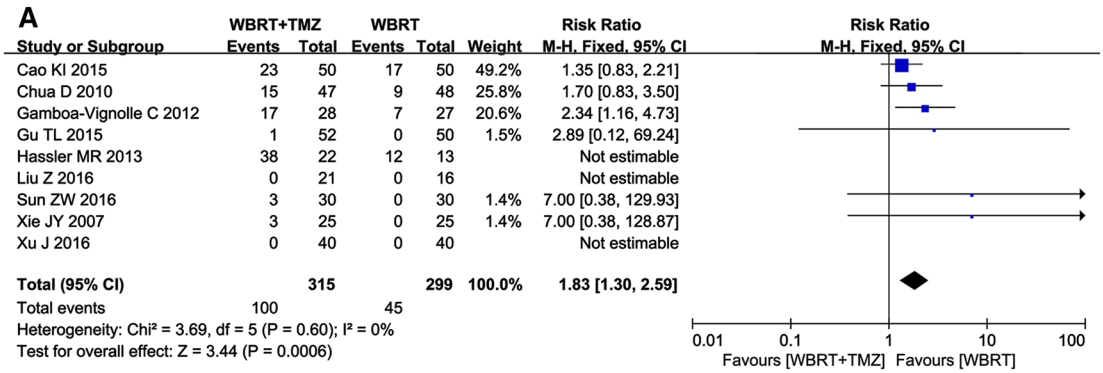


Fig. 2 Analysis of objective response rate (ORR). **a** ORR of 13 RCTs. Subgroup analysis of RCTs in Chinese or non-Chinese patients. **b** Subgroup analysis of RCTs in NSCLC or breast cancer patients



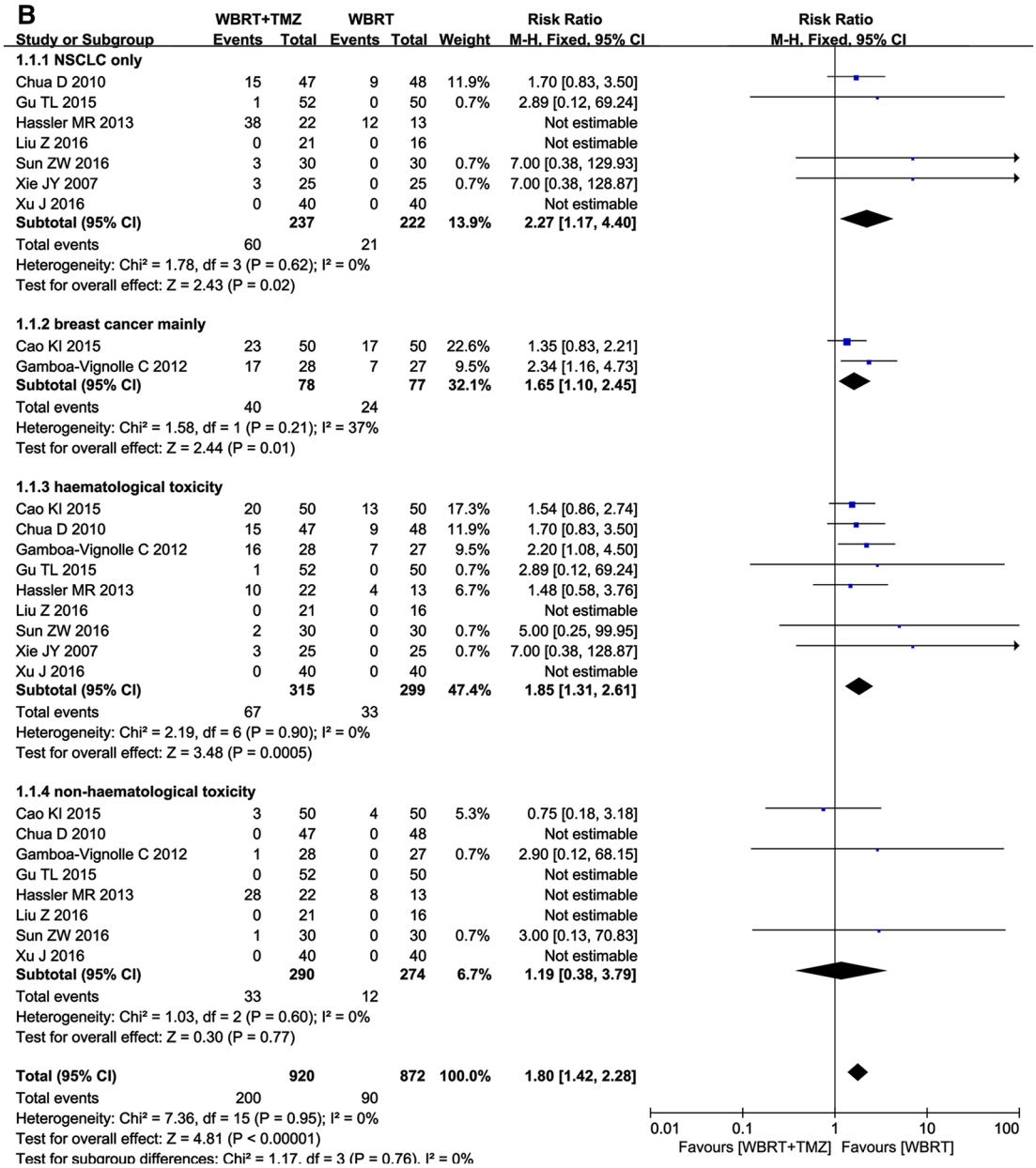


Fig. 3 Analysis of toxicity rates. **a** Overall toxicity rates. **b** Subgroup analysis of toxicity in NSCLC or breast cancer patients; hematological toxicity or non-hematological toxicity

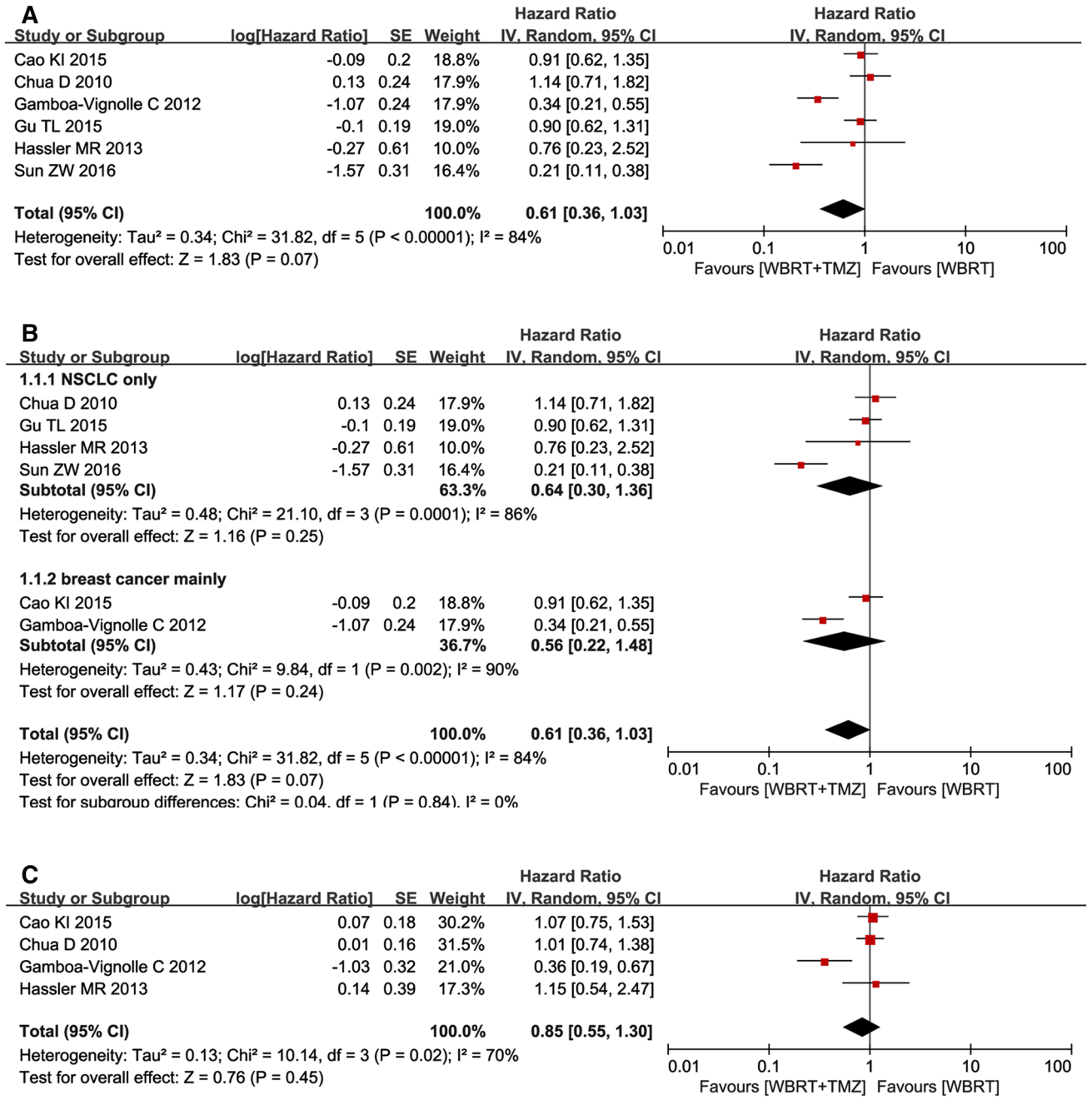


Fig. 4 Analysis of overall survival (OS) and progression-free survival (PFS). **a** Overall survival in 6 RCTs. **b** Subgroup analysis of OS in NSCLC or breast cancer patients. **c** Analysis of PFS in 4 RCTs

clear evidence [26]. Among the 14 randomized clinical trials included in this study, ORR was used in all the trials, and OS was used in only six trials (Table 1). Our results suggested that ORR did not correlate completely with OS, which may be because of the limited availability of information on subsequent treatment and the effect of the small sample size on the reliability of results.

The addition of TMZ to WBRT has shown a significant benefit in ORR in the treatment of NSCLC patients with brain metastasis but not in breast cancer patients, indicating that the therapeutic effects are dependent on the site of primary cancer. Our study results are consistent with an earlier multi-center phase II study which evaluated the combination of WBRT and TMZ versus WBRT alone in NSCLC and breast cancer patients (breast cancer: 2 out of 51 versus NSCLC: 3 out of 53) [27]. However, another phase II trial of temozolomide using protracted low-dose and whole brain radiotherapy demonstrated opposite results, showing that the

ORR in breast cancer was much better than that in NSCLC (breast cancer: 7 out of 12 versus NSCLC: 6 out of 15) [28]. When administered in conjunction with radiotherapy and as a maintenance therapy, TMZ was shown to significantly improve the survival of patients with newly diagnosed glioblastoma [29]. Treatment of recurrent malignant gliomas and brain metastases has not been standardized. The DNA repair protein *O*6-methylguanine-DNA methyltransferase (MGMT), which is a key enzyme for predicting the response to both radiotherapy and temozolomide in glioma patients, can cause resistance to TMZ. A phase II study assessing the efficacy of TMZ in relapsed small cell lung cancer (SCLC) linked the status of MGMT promoter methylation with response to therapy [30]. Promoter methylation of MGMT has been detected in 21–26% of NSCLC biopsies [31, 32]. MGMT was found to be hypomethylated in stage II, III and IV invasive breast cancer. MGMT methylation levels were low and appeared to decrease with tumor stage [33]. This may explain the discrepancy between the response of NSCLC and breast cancer patients to the combined therapy of WBRT and TMZ. Given the contradictory results, combined therapy of WBRT and TMZ for breast cancer patients should be evaluated more cautiously. The status of MGMT promoter methylation may be a predictive biomarker of the response to combination therapy.

Conclusion

No advantages of concurrent WBRT and TMZ were observed in breast cancer patients with brain metastases. Combination therapy was associated with improved ORR in NSCLC patients, especially in Chinese patients. Validated surrogate endpoint ORR may be accepted as evidence for the combination therapy in NSCLC with brain metastasis only when improved ORR predicts better clinical outcomes.

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Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest in this work.

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