Efficacy of different therapies for brain metastases of non-small cell lung cancer: a systematic review and meta-analysis

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Background: As one of the most common causes of death in advanced non-small cell lung cancer (NSCLC), brain metastases (BM) have attracted attention and debate about treatment options, especially for patients with negative driver genes or resistance to targeted agents. Therefore, we conducted a meta-analysis to investigate the potential benefit of different therapeutic regimens for intracranial lesions in non-targeted therapy NSCLC patients.

Methods: A comprehensive search was conducted in databases including PubMed, Embase, and the Cochrane Library. The primary endpoints included the intracerebral objective response rate (icORR) and intracerebral progression-free survival (iPFS) in patients with BM.

Results: Thirty-six studies involving 1,774 NSCLC patients with baseline BM were included in this meta-analysis. Antitumor agents plus radiotherapy (RT) showed the most significant synergistic effects; the highest pooled icORR that appeared in the combination of immune checkpoint inhibitor (ICI) and RT was 81% [95% confidence interval (CI): 16–100%], and the median iPFS was 7.04 months (95% CI: 2.54–11.55 months). The pooled icORR and median iPFS of RT plus chemotherapy were 46% (95% CI: 34–57%) and 5.7 months (95% CI: 3.90–7.50 months), respectively. The highest median iPFS in nivolumab plus ipilimumab plus chemotherapy was 13.5 months (95% CI: 8.35–18.65 months). ICI plus chemotherapy also showed potent antitumor activity in BM, with a pooled icORR of 56% (95% CI: 29–82%) and a median iPFS of 6.9 months (95% CI: 3.20–10.60 months). Notably, the subgroup analysis indicated that the pooled icORR of patients in programmed cell death-ligand 1 (PD-L1) (≥50%) who received ICI was 54% (95% CI: 30–77%), and that of patients who received first-line ICI was 69.0% (95% CI: 51–85%).

Conclusions: ICI-based combination treatment provides a long-term survival benefit for non-targeted therapy patients, with the most significant benefits observed in improving icORR and prolonging overall survival (OS) and iPFS. In particular, patients who received first-line treatment or who were PD-L1-positive had a more significant survival benefit from aggressive ICI-based therapies. For patients with a PD-L1-negative status, chemotherapy plus RT led to better clinical outcomes than other treatment regimens. These innovative findings could help clinicians to better select therapeutic strategies for NSCLC patients with BM.

Keywords: Non-small cell lung cancer (NSCLC); brain metastasis (BM); antitumor agents; immune checkpoint inhibitors (ICIs); meta-analysis

Introduction

Despite the recent progress in therapeutic strategies for metastatic non-small cell lung cancer (NSCLC), the prognosis of NSCLC patients with brain metastases (BM), which is one of the most common metastatic sites and fatal factors, has failed to show substantial improvements. Without effective treatment, the overall survival (OS) of such patients ranges from several weeks to several months. However, the selectivity of the blood-brain barrier (BBB) limits the delivery of drugs to the brain parenchyma during systemic therapy, and the prognosis also relies on several essential characteristics of intracranial lesions, such as the number, size, locations, and central nervous system (CNS) symptoms (1). Generally, patients choose radiotherapy (RT) or surgery to rapidly alleviate their neurological symptoms. Among the systemic therapies, which include chemotherapy, angiogenesis inhibitors, immune checkpoint inhibitors (ICIs), and targeted agents, the latter are the best choice

for patients with molecular drivers (2). However, there is an ongoing concern and debate about the optimal therapies for BM patients with negative driver genes or resistance to tyrosine kinase inhibitors (TKI) (3).

Unfortunately, few trials have evaluated the clinical benefits of systemic therapies for intracranial lesions in NSCLC patients who cannot benefit from targeted therapy. Traditionally, chemotherapy is reserved as a salvage therapy for BM because the BBB resists the passage of chemotherapeutic agents. Thus far, several chemotherapeutic agents, such as paclitaxel, vinorelbine or gemcitabine, cisplatin, and others, seem to be effective for CNS lesions (4). Currently, ICI-combined therapies are widely considered for patients with NSCLC. However, patients with BM are excluded from most clinical trials on programmed cell death-1 (PD-1) or programmed cell death-ligand 1 (PD-L1) inhibitors. KEYNOTE-189, which included the most extensive subgroup analysis of patients with BM, reported that the OS of patients treated with pembrolizumab combined with chemotherapy was significantly superior to those subjected to pure chemotherapy [hazard ratio (HR) =0.36; 95% confidence interval (CI): 0.20–0.62] (5,6).

A better understanding of the activity of different antitumor agents in the CNS is very important for making the optimal clinical choice. Therefore, in this study, we performed a meta-analysis to make reasonable suggestions for clinical treatment by comparing different therapies and assessing the most effective strategies for intracranial lesions in non-targeted therapy NSCLC patients. This meta-analysis was reported in accordance with the PRISMA reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-515/rc) (7).

Methods

From January 1, 2005, to October 1, 2021, the relevant information was systematically searched in the Embase, PubMed, and Cochrane Library electronic databases. Furthermore, we searched for abstracts from meetings of the European Society for Medical Oncology, the World Conference on Lung Cancer, and the American Society of Clinical Oncology. The following search terms were

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Highlight box

Key findings

- Our study found that non-small cell lung cancer (NSCLC) patients with brain metastases (BM) who received immune checkpoint inhibitor (ICI)-based therapies achieved an impressive intracerebral objective response rate (icORR) and long-term survival benefit. In particular, patients who received first-line treatment or were programmed death-ligand 1 (PD-L1)-positive could benefit more from ICIs.

What is known and what is new?

- There is an ongoing concern and debate about the optimal therapies for BM patients with negative driver genes.
- Our study improves the understanding of different treatments in NSCLC patients with BM, suggesting that ICI-based therapies have potential clinical value for BM.

What are the implications, and what should change now?

- These results could help clinicians to select an optimal combination strategy for NSCLC patients with BM. Therapeutic strategies in these patients should be individualized based on their clinical characteristics. However, more prospective clinical trials are still needed to evaluate the efficacy and safety of different treatments in advanced patients with baseline BM.
- Report here about implications and actions needed.

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used: "(lung cancer or non-small cell lung cancer or NSCLC or lung adenocarcinoma or lung squamous)" and "(immunotherapy or immune checkpoint inhibitors or nivolumab or pembrolizumab or atezolizumab or durvalumab or nivolumab or ipilimumab or PD-1 or PD-L1) or (chemotherapy) or (angiogenesis inhibitors or bevacizumab) or (radiotherapy or radiation or radiosurgery)" and "(brain metastases or central nervous system)".

Inclusion criteria

The inclusion criteria were as follows: (I) randomized controlled trials, non-randomized clinical trials, prospective or retrospective observational studies, or abstracts; (II) articles involving patients diagnosed with BM of NSCLC who received non-targeted therapy; (III) the study endpoints included the intracerebral objective response rate (icORR) or intracerebral progression-free survival (iPFS); and (IV) the proportion of patients with epidermal growth factor receptor (EGFR) gene or Kirsten rat sarcoma viral oncogene (KRAS) mutation did not exceed 25%.

The exclusion criteria were as follows: (I) case reports, reviews, editorials, meta-analyses, commentaries, and letters; and (II) studies that did not focus on any of the abovementioned endpoints.

Data extraction

Two researchers independently extracted information from the eligible studies on non-targeted therapy NSCLC patients with BM, including their clinical characteristics and outcomes. Specifically, sex, age, gene-mutation status, study type, Eastern Cooperative Oncology Group (ECOG) score, smoking, corticosteroid use, clinical treatments, histological type, line of treatment, percentage of asymptomatic nervous lesions, intracranial lesion status, and PD-L1 status were recorded. The main observational indicators were the intracranial outcomes, including icORR [defined as the proportion of patients reaching intracranial complete or partial response (PR) among the total number of NSCLC patients with BM] and iPFS. The OS was not regarded as an observational indicator because the influence of factors such as subsequent treatment and medical cost was complex. For each eligible study, the risk of bias was assessed by the Newcastle-Ottawa scale, and the score ranged from 0 to 9.

Statistical analysis

We used descriptive statistics to summarize the clinical characteristics obtained from the eligible studies (*Table 1*). We performed a meta-analysis using the random-effects method (I–V heterogeneity) following Freeman-Tukey double arcsine transformation with 95% CI. Statistical heterogeneity was assessed using the I^2 test in the random-effects model. $P<0.1$ or $I^2>50\%$ was considered to express significant heterogeneity. The significance of the difference in the pooled effect size was examined using the Z-test. All of the P values were two-sided, and $P<0.05$ was considered statistically significant. We also performed a sensitivity analysis to evaluate the stability of the results by sequentially excluding each study. Publication bias was evaluated with the funnel plot asymmetry test. The data analysis was performed by using R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria) and Stata software version 15.1 (Stata Corporation, College Station, TX, USA).

Results

Characteristics of the included studies

A total of 3,713 records were obtained in the initial database search, and 864 duplicate studies were removed. After manually screening the abstracts and references, 36 studies were included after the final selection according to the eligibility criteria (*Figure 1*). Among these, 21 studies were retrospective and 15 were prospective trials. The therapeutic regimens included pure ICI (8-17), pure chemotherapy, chemotherapy plus bevacizumab, ICI plus RT, chemotherapy plus RT, ICI plus chemotherapy, nivolumab plus ipilimumab and RT, and nivolumab plus ipilimumab plus chemotherapy (18-36). Seven studies that only included iPFS data were also included (37-43).

These studies included a total of 1,774 patients who received eight different treatments, and all of the patients received whole-brain radiotherapy (WBRT) in the chemotherapy plus RT subgroup (41). As for the ICI plus RT subgroup, one study administered stereotactic radiosurgery (SRS), while another divided patients into two groups according to WBRT or SRS. We considered the two groups as a whole in the subgroup analysis based on the type of therapies. The details for each trial are shown in *Tables 1,2*. The proportion of the population with driver-gene mutation was required to be <25% in each study, except for one study where patients with EGFR or KRAS

Table 1 Baseline characteristics of NSCLC patients with BM in the included studies

Author	Year	Type	Therapy regimen	Treatment line	Sex (F/M), %	Median age	Smoke %	Response Assessment method	ECOG 0–1, %	Refs
Sun L	2021	Retro	Pembro	≥1	47.6/52.4	66	85.7	–	82.5	(8)
Goldberg SB	2020	Pro	Pembro	≥1	33/67	60	93	mRECIST	100	(9)
Gauvain C	2018	Retro	Nivo	≥1	24/76	59.5	91	RECIST 1.1	–	(10)
Dudnik E	2016	Retro	Nivo	–	60/40	78	80	mRECIST 1.1	–	(11)
Hendriks L	2019	Retro	ICI	–	62/28	61.5	93.4	NS	77.2	(12)
Wakuda K	2021	Retro	Pembro	1	74/26	70	91	RECIST 1.1	39	(13)
Zhang GW	2020	Retro	Nivo	≥2	78/22	57.7	–	RECIST 1.1	84	(14)
Song P	2019	Retro	ICI	–	–	–	–	RECIST 1.1	–	(15)
Skribek M	2020	Retro	ICI	≥1	54.9/45.1	69	86.3	mRECIST 1.1	75.8	(16)
Kitai H	2013	Retro	Chem	–	44.4/55.6	63	48	–	–	(17)
Barlesi F	2011	Pro	PP	1	67.4/32.6	60.4	–	RECIST	97.7	(18)
Chouahnia K	2010	Pro	PP	–	–	–	–	–	100	(19)
Hu Q	2011	Retro	Chem	–	–	–	–	–	–	(20)
			Chem + WBRT	–	–	–	–	–	–	
Bailon O	2012	Pro	PP	1	70/30	58	–	RECIST	90	(21)
Bearz A	2010	Retro	Pemetrex	–	–	–	–	RECIST	–	(22)
Monnet I	2020	Pro	PP + Bev	1	78.3/22.7	60.5	89.2	RECIST 1.1	100	(23)
Tian Y	2019	Retro	PP	1	40/60	54	24.4	RECIST 1.1	–	(24)
			PP + Bev	1	61.5/38.5	58	26.9	NA	–	
Li X	2019	Retro	PP	1	–	–	–	RECIST 1.1	–	(25)
			PP + Bev	1	–	–	–	–	–	
Besse B	2015	Pro	TP + Bev	1	69/31	61	79	RECIST 1.0	100	(26)
Ashinuma H	2014	Retro	Chem + Bev	–	50/50	62.5	–	RECIST 1.1	–	(27)
Hirano S	2006	Retro	Chem	1	52.6/47.4	61	–	RECIST 1.1	–	(28)
Metro G	2021	Retro	Pembro	1	44.4/55.6	74	77.8	mRECIST1.1	88.9	(29)
			Pembro + WBRT	1	37.5/62.5	63	87.5	mRECIST 1.1	–	
			Pembro + SRS	1	76.9/22.1	69	92.3	mRECIST 1.1	–	
Shepard MJ	2019	Retro	ICI + SRS	–	64.7/35.3	64.4	–	RANO-BM	–	(30)
Afzal MZ	2018	Retro	PP + Pembro	≥1	–	63.7	100	RECIST 1.1	82.4	(31)
He Q	2017	Pro	PP + WBRT	1	34.4/65.6	58	31.3	RANO-BM	–	(32)
Dinglin XX	2013	Pro	PP + WBRT	≥1	64.3/35.7	55.4	54.8	RECIST 1.0	100	(33)
Quantin X	2010	Pro	Chem + WBRT	–	75.7/24.3	59.1	–	RECIST	–	(34)
				–	75.8/24.2	56	–	–	–	
Chen L	2009	Pro	Chem + WBRT	≥1	60.8/39.2	53	–	RECIST	–	(35)

Table 1 (*continued*)

Table 1 (*continued*)

Author	Year	Type	Therapy regimen	Treatment line	Sex (F/M), %	Median age	Smoke %	Response Assessment method	ECOG 0–1, %	Refs
Lee DH	2008	Pro	Chem (earlier) + WBRT	1	76/24	60	–	WHO	100	(36)
			Chem + WBRT (earlier)	1	83/17	62	–	WHO	95.6	
Carbone D	2021	Pro	Pembro + Ipili + Chem	1	31.4/68.6	61	78	mRECIST 1.1	98	(37)
			Chem	1	48/52	64	92	mRECIST 1.1	100	
Lau SCM	2021	Retro	ICI + RT	–	47/53	64	77	RECIST 1.1	92	(38)
			Chem + RT	–	51/49	62	67	RANO−BM	88	
Lim SH	2015	Pro	Chem + SRS (earlier)	–	71/29	58	58	RECIST 1.1	100	(39)
			Chem (earlier) + SRS	–	73/27	57	65		100	
Azzam G	2018	Retro	ICI + SRS	–	–	–	–	–	–	(40)
Li J	2020	Pro	Pembro + ipili + SRS	–	–	–	–	–	–	(41)
Lee M	2021	Retro	ICI	–	62.5/27.5	61	–	–	92.3	(42)
			ICI + RT (concurrent)	–	80/20	62	–	–	100	
			ICI + RT (non-concurrent)	–	70/30	59	–	–	100	
Nadal E	2019	Pro	ICI + Chem	–	29/71	–	75	RANO−BM	65	(43)

NSCLC, non-small cell lung cancer; BM, brain metastases; F, female; M, male; ECOG, Eastern Cooperative Oncology Group; Refs, references; Retro, retrospective; Pro, prospective; ICI, immune checkpoint inhibitor, Chem, chemotherapy; Pembro, pembrolizumab; Nivo, nivolumab; Ipili, ipilimumab; PP, pemetrexed plus cisplatin; TP, paclitaxel plus cisplatin; Bev, bevacizumab; No-sq, no-squamous; RT, radiotherapy; WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery.

mutations reached 40.5% of the total population. That study reported the results of intracranial lesions in NSCLC patients with BM treated with pure ICI, which was the largest group (255 patients) examined in our study (12). Considering that the reported icORR was similar to the results of an important prospective study by Goldberg *et al.*, we decided to include this study in the final analysis (9).

Meta-analysis of the pooled icORR: all patients

We extracted the icORR and iPFS from the included 36 studies involving a total of 1,774 patients. Unfortunately, significant heterogeneity was observed in each subgroup, which may be attributable to the specificity of the single-arm study. Therefore, the random-effect model was adopted. We performed comparisons of the pooled icORR in different treatment subgroups, which ranged from 33% to 81% (*Figure 2A*). The most significant effect was observed in the ICI combined with RT subgroup, where the pooled icORR was 81% (95% CI: 16–100%, P=0.000), and the worst effect was found in the pure chemotherapy subgroup (33%, 95% CI: 24–42%, P=0.000). The pooled icORR was 56% (95% CI: 29–82%, P=0.000) in the ICI plus chemotherapy subgroup, 46% (95% CI: 34–57%, P=0.000) in the chemotherapy plus RT subgroup, 44% (95% CI: 23–66%, P=0.000) in the chemotherapy plus bevacizumab subgroup, and 34% (95% CI: 23–46%, P=0.000) for the ICI subgroup. Notably, although double ICI plus chemotherapy was only reported in one study, its icORR reached 51.3%, demonstrating the efficacy of double ICI combination therapy against BM. A more intuitive comparison of icORR is presented in *Figure 2B*.

Meta-analysis of pooled icORR: PD-L1 status

Five of the 10 studies in the ICI subgroup divided patients based on PD-L1 status. Therefore, a subgroup analysis was performed to explore the possible correlation between PD-L1 status and the effect of immunotherapy, and the heterogeneity ranged from 0% to 58%. The pooled results revealed a significant difference between the groups based on the different PD-L1 expressions. The pooled icORR
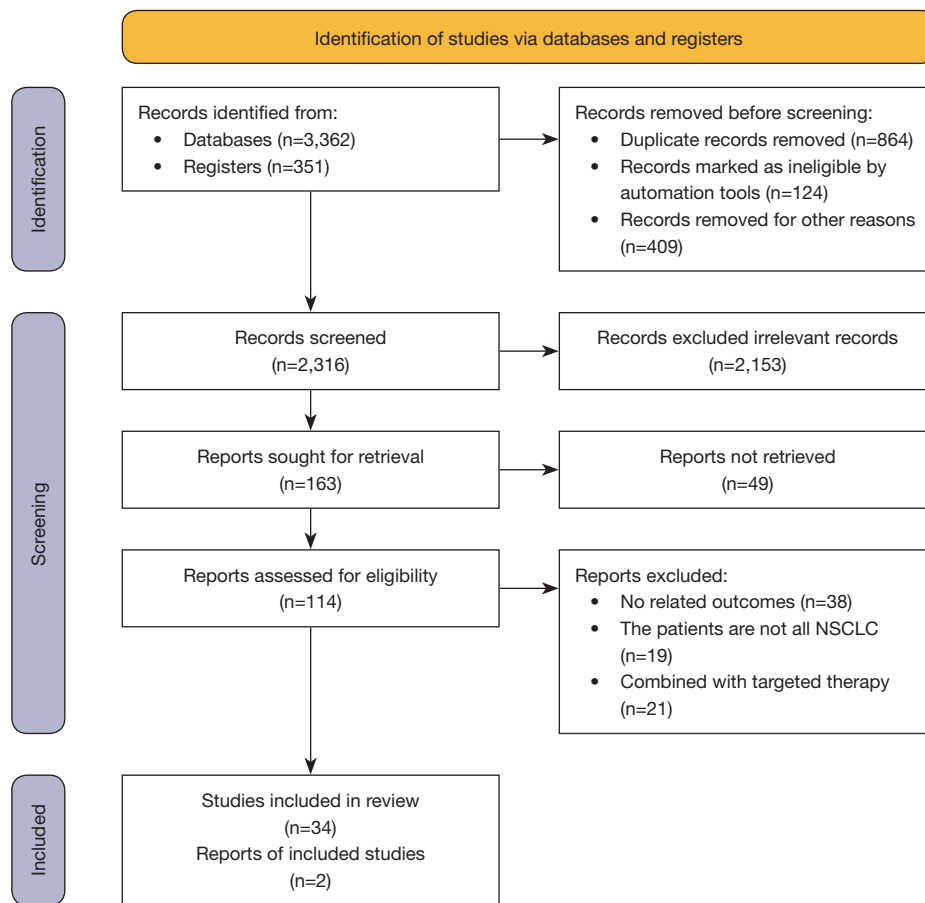
Figure 1 Flowchart diagram of the literature search and study selection. NSCLC, non-small cell lung cancer.

**Table 2** Clinical characteristics of NSCLC patients with BM of studies

Author	Year	PD-L1 ≥1, %	Steroid, %	Number of BM, %	CNS symptom, %	Treated BM, %	Dose	Refs
Sun L	2021	–	–	–	–	60.30	–	(8)
Goldberg SB	2020	–	–	100% 1–5	–	67	–	(9)
Gauvain C	2018	–	–	76% 1–3	–	–	–	(10)
Dudnik E	2016	–	0	–	–	–	–	(11)
Hendriks L	2019	61.5	27.4	47% 1–3	14.7	82.2	–	(12)
Wakuda K	2021	–	–	–	–	57	–	(13)
Zhang GW	2020	–	–	–	–	50	–	(14)
Song P	2019	–	–	–	–	–	–	(15)
Skribek M	2020	80	54.1	63.6% 1–3	54.5	78.8	–	(16)
Kitai H	2013	–	–	–	–	–	–	(17)
Barlesi F	2011	–	–	–	0	–	–	(18)
Chouahnia K	2010	–	–	–	–	–	–	(19)

Table 2 (*continued*)

Table 2 (*continued*)

Author	Year	PD-L1 ≥1, %	Steroid, %	Number of BM, %	CNS symptom, %	Treated BM, %	Dose	Refs
Hu Q	2011	–	–	–	–	–	–	(20)
Bailon O	2012	–	63	60% 1–3	72	0	–	(21)
Bearz A	2010	–	–	–	–	–	–	(22)
Monnet I	2020	–	–	93.5% 1–5	–	0	–	(23)
Tian Y	2019	–	–	–	42.2	–	–	(24)
		–	–	–	34.6	–	–	
Li X	2019	–	–	–	–	–	–	(25)
Besse B	2015	–	–	100% 0–2	–	–	–	(26)
Ashinuma H	2014	–	–	–	–	80	–	(27)
Hirano S	2006	–	–	31.6% 1–2	–	–	–	(28)
Metro G	2021	–	11.1	66.7 % 1–3	–	–	–	(29)
		100	37.5	12.5% 1–3	–	0	–	
		100	38.5	68.2% 1–3	–	0	–	
Shepard MJ	2019	76.5	58.80	–	–	35.4	Median 19	(30)
Afzal MZ	2018	–	–	–	–	50	–	(31)
He Q	2017	–	–	34% 1–2	–	–	30	(32)
Dinglin XX	2013	–	100	28.6% 1–2	–	–	30	(33)
Quantin X	2010	–	–	59.5 % 1–2	–	–	54	(34)
		–	–	51.2 % 1–2	–	–	–	
Chen L	2009	–	–	47.1% 1–3	–	–	30–60	(35)
Lee DH	2008	–	–	–	0	–	–	(36)
		–	–	–	0	–	30	
Carbone D	2021	64	6	–	–	36	–	(37)
		67	16	–	–	45	–	
Lau SCM	2021	–	–	–	44	–	–	(38)
		–	–	–	39	–	–	
Lim SH	2015	–	–	Median 2	0	0	–	(39)
		–	–	Median 1.82	0	0	–	
Azzam G	2018	–	–	–	–	–	–	(40)
Li J	2020	–	–	–	–	–	–	(41)
Lee M	2021	30.8	–	Median 2	–	15.4	–	(42)
		58.3	–	Median 2	–	12.5	Median 19	
		29.6	–	Median 2	–	11.1	–	
Nadal E	2019	–	–	–	–	–	–	(43)

NSCLC, non-small cell lung cancer; BM, brain metastases; Refs, references; PD-L1, programmed cell death ligand-1; CNS, central nervous system.
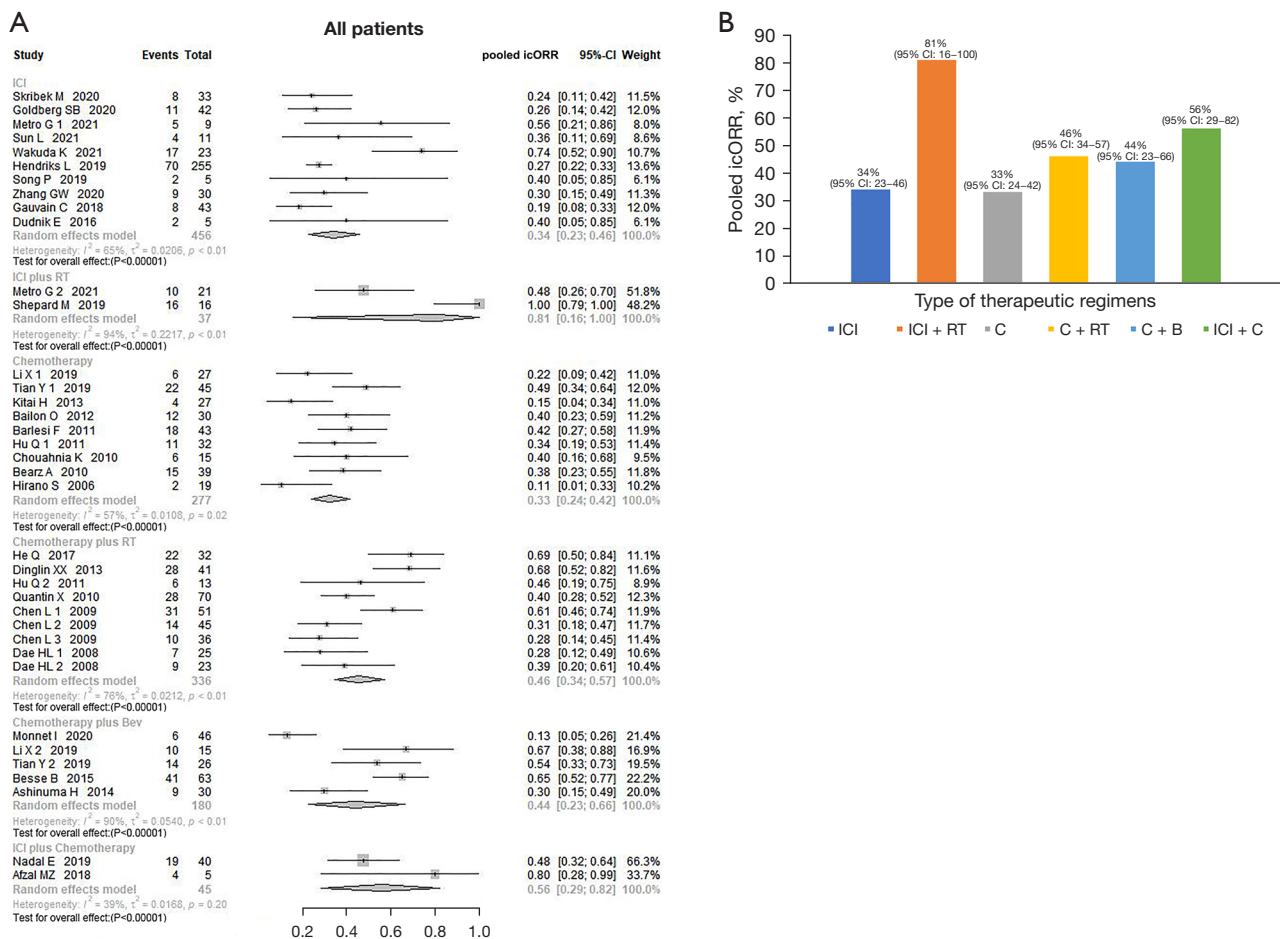
Figure 2 icORR of brain metastasis in NSCLC patients for comparing the different treatment subgroups. (A) Forest plots of icORR, (B) bar plot of icORR. icORR, intracerebral objective response rate; NSCLC, non-small cell lung cancer; ICI, immune checkpoint inhibitor; RT, radiotherapy; Bev, bevacizumab; ICI+RT, immune checkpoint inhibitor plus radiotherapy; C, chemotherapy; C+RT, chemotherapy plus radiotherapy; C+B, chemotherapy plus bevacizumab; ICI+C, immune checkpoint inhibitor plus chemotherapy.

was 2.0% (95% CI: 0–12%, P=0.676) in the PD-L1 expression <1% subgroup, suggesting that pure ICI was ineffective for BM in this subgroup. The most significant icORR from the PD-L1 ≥50% subgroup was 54% (95% CI: 30–77%, P=0.000). The pooled icORRs of PD-L1 expression ≥1% and 1%≤ PD-L1 <50% were 38% (95% CI: 22–53%, P=0.000) and 30% (95% CI: 0–66%, P=0.114), respectively. Therefore, the beneficial effect of ICI on intracranial lesions may be positively correlated with PD-L1 status (*Figure 3*).

Meta-analysis of pooled icORR: first-line treatment

The icORR data for first-line treatment were provided in 12 studies. The pooled icORRs of the ICI, chemotherapy,

chemotherapy combined with RT, and chemotherapy plus bevacizumab subgroups were 69% (95% CI: 51–85%, P=0.000), 33% (95% CI: 20–47%, P=0.000), 50% (95% CI: 32–68%, P=0.000), and 48% (95% CI: 22–75%, P=0.000), respectively (*Figure 4A*). As for the non-first-line subgroups, the icORR of these patients was 26.0% (95% CI: 21–30%, P=0.000) in the ICI subgroup, 31.0% (95% CI: 20–44%, P=0.000) in the chemotherapy subgroup, and 42.0% (95% CI: 28–57%, P=0.000) in the chemotherapy combined with RT subgroup (*Figure 4B*). Only one study included non-first-line treatment in the chemotherapy plus bevacizumab subgroup, so this group was ruled out in the subsequent analyses. The results demonstrated that the efficacy of ICI for BM showed the most significant improvement in the first-line treatment.
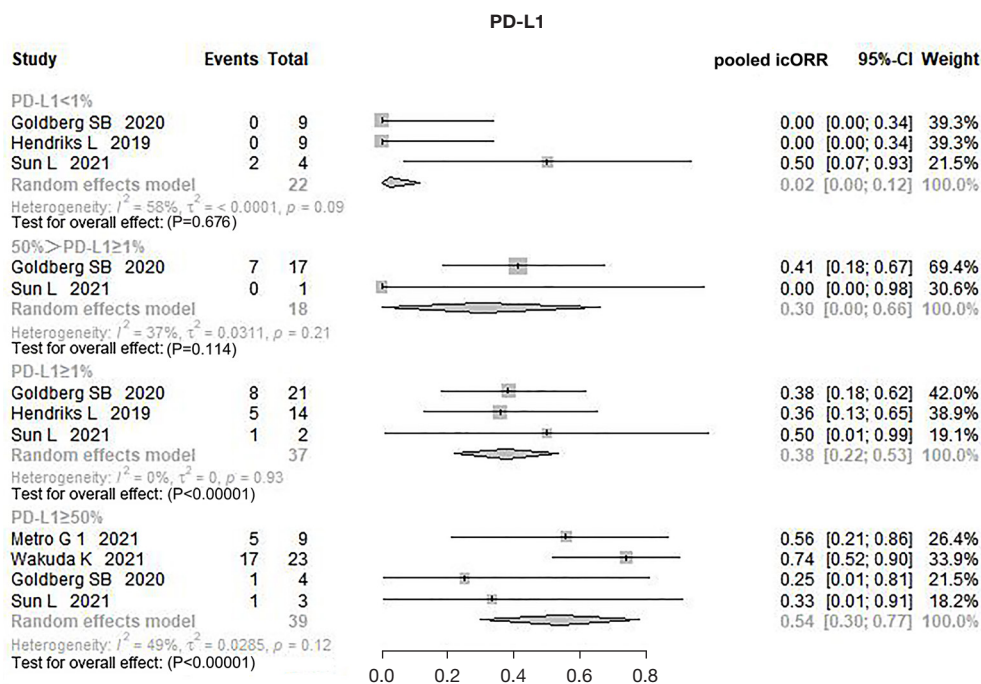
Figure 3 Forest plots of icORR of brain metastasis stratified according to the PD-L1 expression in subgroup NSCLC patients received with immunotherapy. icORR, intracerebral objective response rate; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1.

Meta-analysis of pooled icORR: with or without RT

Notably, subgroup analysis of antitumor agents plus RT compared with antitumor agents alone revealed a significant clinical benefit. The pooled icORR in the combination RT group was 52% (95% CI: 37–67%, P=0.000), as compared with 37% (95% CI: 30–44%, P=0.000) in patients without RT (*Figure 5*). We conducted further analysis on ICI plus RT according to the different types of RT (*Figure 6*). The pooled icORR was 75% (95% CI: 1–100%, P=0.054) for ICI plus SRS and 75% (95% CI: 35–97%, P=0.000) for ICI plus WBRT. As only one study was included, this was not sufficient to perform a subgroup analysis.

Meta-analysis of pooled icORR: prospective and retrospective

We performed further analyses of the pooled icORR according to the different types of studies (*Figure 7*). In the chemotherapy subgroup, the prospective arm showed a higher pooled icORR than the retrospective arm: 41% (95% CI: 31–52%, P=0.000) *vs.* 29% (95% CI: 17–41%, P=0.000). In contrast, a higher pooled icORR in the retrospective arm

was observed in the ICI subgroup, 35% (95% CI: 23–49%, P=0.000) *vs.* 26% (95% CI: 14–42%, P=0.000). This may be explained by the inherent shortcomings of retrospective analyses, and further prospective trials are required to guide the selection of clinical therapeutic regimens. Other subgroups were not included in this analysis due to sample size limitations.
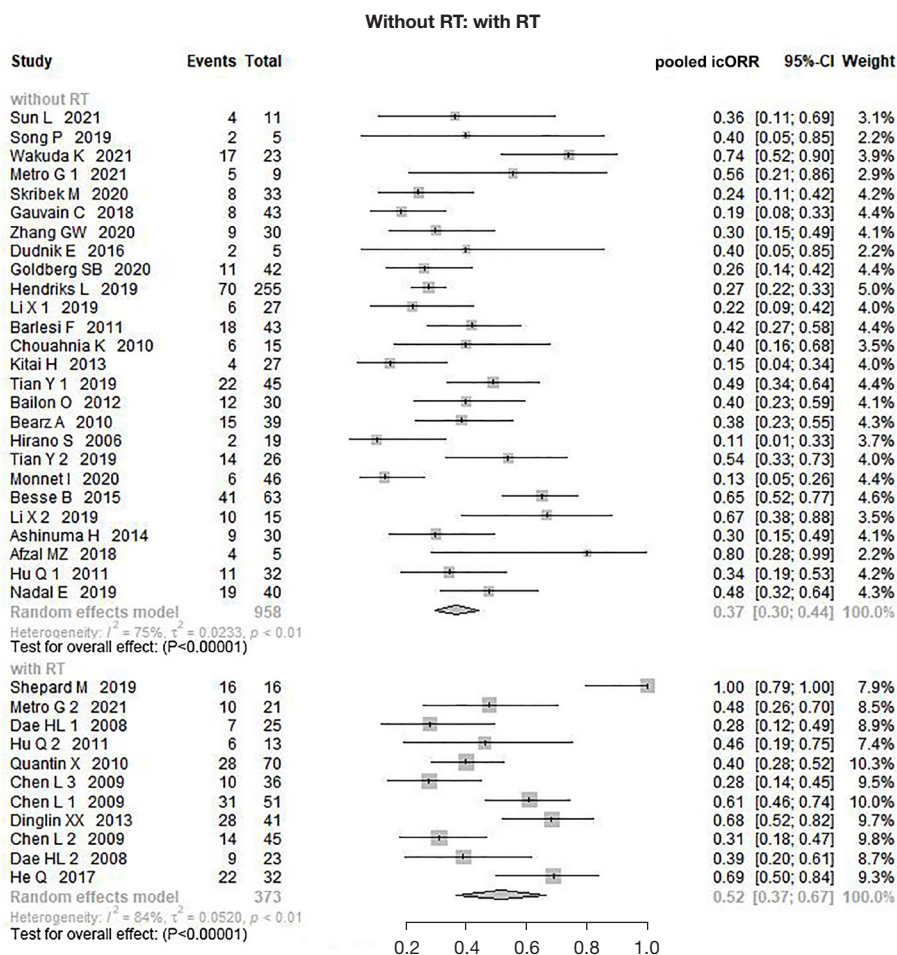
Discordance

Five studies offered data on the inconsistent response rate of primary and metastatic lesions, and the discordance response rate ranged from 12.7% to 60%.
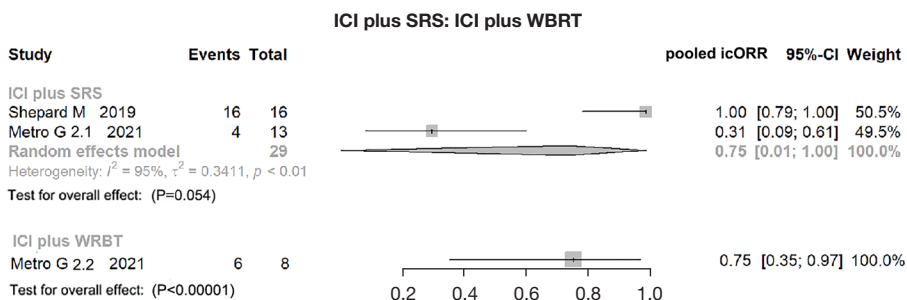
Meta-analysis of pooled iPFS

Due to the limitations of single-arm meta-analyses, only five subgroups provided sufficient data to perform an iPFS analysis (*Figure 8*). Since the difference of the pooled iPFS was statistically significant (P=0.000), we assessed the intracranial long-term survival benefit by comparing the pooled iPFS. The results showed that the highest median iPFS was 13.5 months (95% CI: 8.35–18.65 months) in patients who
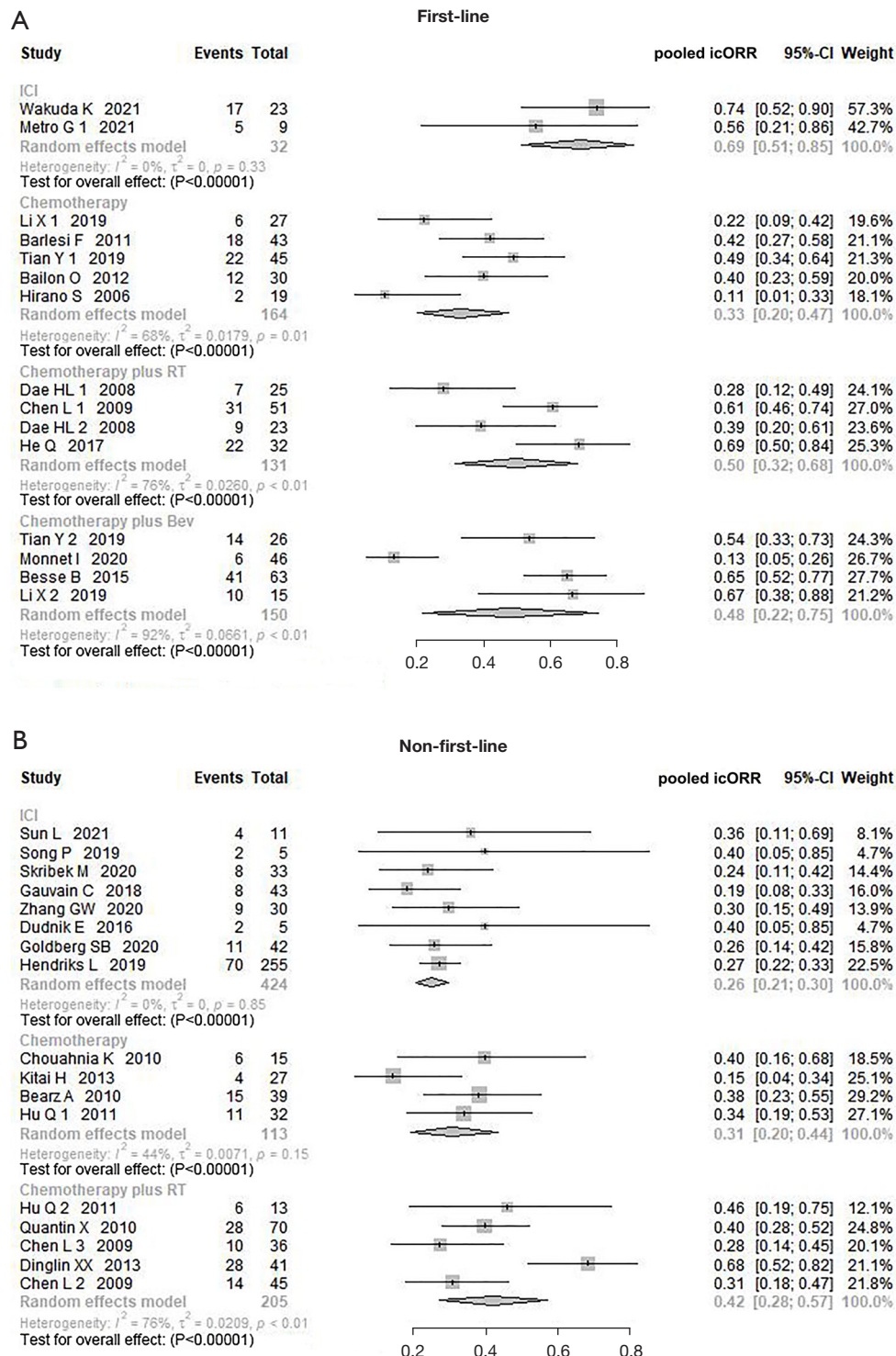
Figure 4 Forest plots of icORR of brain metastasis in NSCLC patients based on different treatment-line subgroups. (A) First-line treatment. (B) Non-first-line treatment. icORR, intracerebral objective response rate; ICI, immune checkpoint inhibitor; RT, radiotherapy; Bev, bevacizumab; NSCLC, non-small cell lung cancer.

Without RT: with RT

| Study	Events	Total		pooled icORR	95%-CI	Weight
without RT						
Sun L 2021	4	11		0.36	[0.11; 0.69]	3.1%
Song P 2019	2	5		0.40	[0.05; 0.85]	2.2%
Wakuda K 2021	17	23		0.74	[0.52; 0.90]	3.9%
Metro G 1 2021	5	9		0.56	[0.21; 0.86]	2.9%
Skribek M 2020	8	33		0.24	[0.11; 0.42]	4.2%
Gauvain C 2018	8	43		0.19	[0.08; 0.33]	4.4%
Zhang GW 2020	9	30		0.30	[0.15; 0.49]	4.1%
Dudnik E 2016	2	5		0.40	[0.05; 0.85]	2.2%
Goldberg SB 2020	11	42		0.26	[0.14; 0.42]	4.4%
Hendriks L 2019	70	255		0.27	[0.22; 0.33]	5.0%
Li X 1 2019	6	27		0.22	[0.09; 0.42]	4.0%
Barlesi F 2011	18	43		0.42	[0.27; 0.58]	4.4%
Chouahnia K 2010	6	15		0.40	[0.16; 0.68]	3.5%
Kitai H 2013	4	27		0.15	[0.04; 0.34]	4.0%
Tian Y 1 2019	22	45		0.49	[0.34; 0.64]	4.4%
Bailon O 2012	12	30		0.40	[0.23; 0.59]	4.1%
Bearz A 2010	15	39		0.38	[0.23; 0.55]	4.3%
Hirano S 2006	2	19		0.11	[0.01; 0.33]	3.7%
Tian Y 2 2019	14	26		0.54	[0.33; 0.73]	4.0%
Monnet I 2020	6	46		0.13	[0.05; 0.26]	4.4%
Besse B 2015	41	63		0.65	[0.52; 0.77]	4.6%
Li X 2 2019	10	15		0.67	[0.38; 0.88]	3.5%
Ashinuma H 2014	9	30		0.30	[0.15; 0.49]	4.1%
Afzal MZ 2018	4	5		0.80	[0.28; 0.99]	2.2%
Hu Q 1 2011	11	32		0.34	[0.19; 0.53]	4.2%
Nadal E 2019	19	40		0.48	[0.32; 0.64]	4.3%
Random effects model		958		0.37	[0.30; 0.44]	100.0%
Heterogeneity: $I^2 = 75\%$, $\tau^2 = 0.0233$, $p < 0.01$						
Test for overall effect: (P<0.00001)						
with RT						
Shepard M 2019	16	16		1.00	[0.79; 1.00]	7.9%
Metro G 2 2021	10	21		0.48	[0.26; 0.70]	8.5%
Dae HL 1 2008	7	25		0.28	[0.12; 0.49]	8.9%
Hu Q 2 2011	6	13		0.46	[0.19; 0.75]	7.4%
Quantin X 2010	28	70		0.40	[0.28; 0.52]	10.3%
Chen L 3 2009	10	36		0.28	[0.14; 0.45]	9.5%
Chen L 1 2009	31	51		0.61	[0.46; 0.74]	10.0%
Dinglin XX 2013	28	41		0.68	[0.52; 0.82]	9.7%
Chen L 2 2009	14	45		0.31	[0.18; 0.47]	9.8%
Dae HL 2 2008	9	23		0.39	[0.20; 0.61]	8.7%
He Q 2017	22	32		0.69	[0.50; 0.84]	9.3%
Random effects model		373		0.52	[0.37; 0.67]	100.0%
Heterogeneity: $I^2 = 84\%$, $\tau^2 = 0.0520$, $p < 0.01$						
Test for overall effect: (P<0.00001)						

0.2 0.4 0.6 0.8 1.0

Figure 5 Forest plots of icORR for brain metastasis based on the RT and non-RT subgroups. RT, radiotherapy; icORR, intracerebral objective response rate.

ICI plus SRS: ICI plus WBRT

| Study	Events	Total		pooled icORR	95%-CI	Weight
ICI plus SRS						
Shepard M 2019	16	16		1.00	[0.79; 1.00]	50.5%
Metro G 2.1 2021	4	13		0.31	[0.09; 0.61]	49.5%
Random effects model		29		0.75	[0.01; 1.00]	100.0%
Heterogeneity: $I^2 = 95\%$, $\tau^2 = 0.3411$, $p < 0.01$						
Test for overall effect: (P=0.054)						
ICI plus WRBT						
Metro G 2.2 2021	6	8		0.75	[0.35; 0.97]	100.0%
Test for overall effect: (P<0.00001)						

0.2 0.4 0.6 0.8 1.0

Figure 6 Forest plots of icORR of brain metastasis based on ICI plus WBRT and ICI plus SRS. ICI, immune checkpoint inhibitor; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy; icORR, intracerebral objective response rate.

received nivolumab plus ipilimumab and chemotherapy. The median iPFS of ICI plus chemotherapy and ICI plus RT was 6.9 months (95% CI: 3.20–10.60 months) and 7.04 months (95% CI: 2.54–11.55 months), respectively. However, the iPFS of pure ICI in patients with BM was lower than the others, only 2.29 months (95% CI: 1.34–3.24 months). Finally, the median iPFS of chemotherapy plus RT was 5.7 months (95% CI: 3.90–7.50 months).
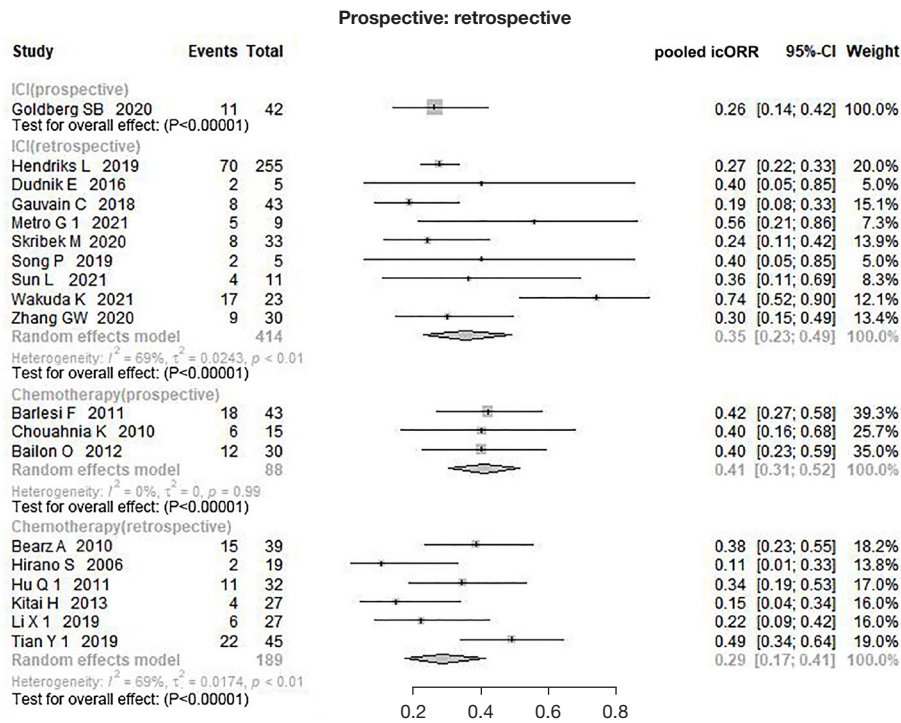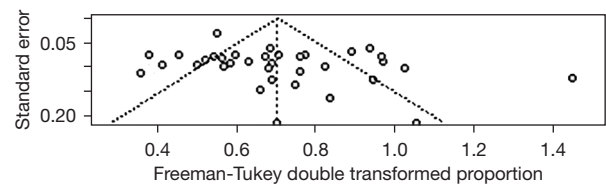
Figure 7 Forest plots of icORR for brain metastasis in NSCLC patients stratified based on the type of studies between the ICI and chemotherapy subgroups. icORR, intracerebral objective response rate; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer.
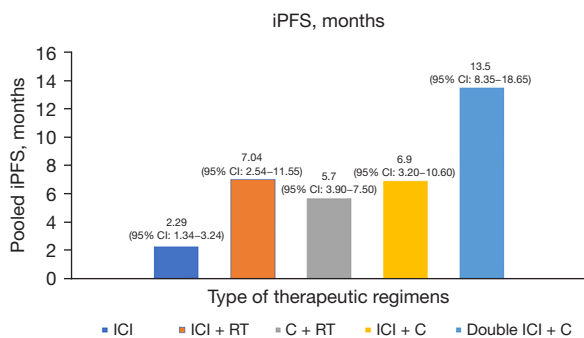
Figure 8 iPFS of NSCLC patients with brain metastasis based on different therapies. iPFS, intracerebral progression-free survival; ICI, immune checkpoint inhibitor; ICI+RT, immune checkpoint inhibitor plus radiotherapy; C+RT, chemotherapy plus radiotherapy; ICI+C, immune checkpoint inhibitor plus chemotherapy; NSCLC, non-small cell lung cancer.

Figure 9 Funnel plot for icORR. icORR, intracerebral objective response rate.

heterogeneity in each subgroup, which was an inevitable limitation of the single-arm study design. Therefore, we decided to include these studies in our analysis.

Discussion

Generally, most clinical trials for NSCLC exclude patients with BM. Although several clinical trials have reported on the long-term survival benefit of NSCLC patients with BM who received immune-based combination therapies, the intracranial efficacy against BM has not yet been elucidated. Alencar *et al.* conducted a meta-analysis to

Publication bias

There was an apparent asymmetry in the funnel plots, which suggested the presence of publication bias (*Figure 9*). However, this finding can be explained by the high

analyze the icORR of NSCLC patients who received pure ICI and revealed that ICI monotherapy was effective for intracranial lesions in NSCLC patients (44). However, considering the limited data in their study, it is difficult to evaluate differences among important clinical features, such as PD-L1 expression, treatment line, and the presence of driver-gene mutations. Most importantly, no studies have compared intracranial efficacy between different therapeutic regimens. Hence, we summarized the current literature and conducted a meta-analysis of intracranial efficacy to improve the understanding of different treatments in NSCLC patients with BM.

Our study suggests that ICI-based therapies have potential clinical value for patients with BM. ICI monotherapy did not show a strong advantage in the control of intracranial lesions, but the impact of the treatment line could explain this finding, considering that most patients who were enrolled in these studies had been treated with non-first-line therapy. Therefore, the analysis could underestimate the real effect of ICI, that is, patients who received ICI monotherapy as first-line treatment had a significant improvement in the pooled icORR, suggesting that early use of ICI is associated with superior BM control.

As the most common biomarker predicting the efficacy of ICI, the PD-L1 expression level in NSCLC patients with BM affected the intracranial efficacy of ICI, even though PD-L1 expression between primary tumors and BM exhibit temporal and spatial heterogeneity. Further analysis suggested limited intracranial efficacy in patients with negative PD-L1 expression. Conversely, the PD-L1 ≥50% subgroup showed the best control of intracranial lesions. The results suggested that PD-L1 status was positively associated with the clinical outcomes of BM, which also represents a significant biomarker for the intracranial prognosis of patients who receive ICI.

In our study, the discordance rate of extracranial and BM responses was between 12.7% and 60%, and the high discrepancy might be a result of the small sample size. As the sample size expanded, the responses of different sites tended to be congruent. Goldberg *et al.* reported a high consistency between BM and primary lesions' PR, and BM PR was present in 8/9 (88%) patients diagnosed with systemic PR. The above-mentioned conclusions preliminarily suggested that ICI might have the same benefit for primary lung tumors and BM lesions in NSCLC (9,45).

Treatment line and PD-L1 expression played an important role in the efficacy of ICI against intracranial lesions, and patients who receive first-line ICI or those with PD-L1 ≥1 may benefit the most. Additionally, the key finding of this meta-analysis is that ICI-combined chemotherapy showed a synergistic effect and higher effectiveness compared to pure ICI. On the one hand, chemotherapy enhanced the efficacy of ICI in the intracranial immune microenvironment by increasing antigen presentation, inducing T-cell proliferation to activate the immune responses of T cells (46). On the other hand, ICI has a slow onset of efficacy, so chemotherapy could help prevent early disease progression before ICI takes effect. In KEYNOTE-407, the systemic objective response rate (ORR) of NSCLC patients with baseline BM who received platinum-doublet chemotherapy with pembrolizumab reached 92.7% (47). The combination of double ICI and chemotherapy provided the added advantage of iPFS and was ranked first in our study. The results consistently indicated that the combination of ICI and chemotherapy is a promising option for NSCLC patients with BM. Several ongoing clinical trials are testing this combined therapy, which will provide us with more evidence to support this conclusion. In the era of immunotherapy, it is worth exploring how to apply combination therapy to reasonably maximize efficacy.

RT still has irreplaceable advantages in the local treatment for BM, especially for severe neurological symptoms, in contrast to the poor results obtained by ICI treatment alone (48-50). In addition, active brain lesions are also a significant poor prognostic factor for NSCLC patients with BM (51). Our study obtained similar results, as BM patients who received ICI alone did not have a significant improvement. We found that ICI plus RT possessed a significant intracranial control, although the number of relevant articles was minimal. Theoretically, this effect could be explained by the following mechanisms: (I) ICI has a synergistic effect with RT (52); and (II) RT may increase the permeability of the BBB (48).

Notably, the synergistic effect between RT and ICI might be a double-edged sword (53), given that patients are at a higher risk of developing radiation necrosis following the combination of ICI with RT (53). In a retrospective study involving 480 patients with BM from various malignancies (including 294 patients with NSCLC) who were treated with RT with or without ICI, a higher incidence of radionecrosis was observed in patients who received ICI plus RT than in those who received RT alone, after adjustment for tumor histopathology (HR, 2.56; 95% CI: 1.35–4.86, P=0.004) (54). Another study involving 180 patients with BM who received SRS and various

systemic therapies, including chemotherapy, ICI, and targeted therapy, showed that the incidence of radionecrosis reached 37.5% in patients who received RT plus ICI, which was significantly higher compared with patients who received targeted therapy or chemotherapy [odds ratio (OR), 2.40; 95% CI: 1.06–5.44, P=0.03] (55). Interestingly, there was a remarkable difference in iPFS between the concurrent- and non-concurrent-treated groups (36,39). Nevertheless, we did not collect sufficient data to assess whether the timing of ICI and RT was the source of these differences (39,42).

Furthermore, the type of RT was also a crucial factor when evaluating the efficacy of ICI combined with RT. Intracranial RT includes WBRT and SRS, and the choice of intracranial RT type depends on the characteristics of BM and the general status of patients. Most studies have suggested that WBRT is the standard option for patients with 5–20 BMs (56), while SRS is the standard option for patients with 1–4 BMs (57). Historically, WBRT has played an important role in the treatment of patients with BM. Compared to SRS, WBRT has significantly improved control of multiple or large intracranial lesions but leads to more neurocognitive function damage and a lower quality of life (58). A prospective trial evaluated the toxicity of WBRT plus SRS by comparing SRS to WBRT plus SRS in patients with BM; the results of this trial showed that patients who received WBRT plus SRS were significantly more likely (52%) to show a decline in neurocognitive function, such as memory and verbal learning, than patients who received SRS alone (24%) (58). There were also significant differences in local control and long-term survival between patients who received ICI plus WBRT and those who received ICI plus SRS. A retrospective analysis of patients with BM who received ipilimumab plus WBRT showed that the rate of intracranial lesion control reached 78% (59). Another retrospective study by Metro *et al.*, which included eight patients who received ICI plus WBRT, 13 patients who received ICI plus SRS, and nine patients who received ICI alone (29), showed that the icORR was 31% in the SRS plus ICI group, 75% in the WBRT plus ICI group, and 55% in the ICI alone group. Moreover, the 12-month survival rates for SRS plus ICI, WBRT plus ICI, and ICI alone were 23.0%, 62.5% and 55.5%, respectively. Currently, clinical data is limited, and some prospective trials comparing ICI plus WBRT to ICI plus SRS have not yet been completed; the results from these ongoing trials may further increase the understanding of different types of ICI plus RT therapeutic regimens.

In our study, we did not observe a significant difference in icORR or iPFS between the WBRT and SRS subgroups, which might be related to data volume limitations. Similar results were obtained in a retrospective study that included 179 driver gene mutation-positive NSCLC patients with BM who received TKIs combined with RT; that is, WBRT did not offer better intracranial control than SRS, and this was probably related to the better systematic tumor control with TKI and ICI compared with pure chemotherapy (60). Another possible reason is the impact of the number of BMs. A study by Chen *et al.* classified 156 NSCLC patients with 1–4 BMs into three groups: those who received SRS, WBRT, and WBRT plus radiotherapy boost (RTB). The median OS and 2-year iPFS rates in the SRS group were not reached and 51.6%, those in the WBRT group were 33.3 months and 42.0%, and those in the WBRT plus RTB group were 27.9 months and 51.1%, respectively (61). There were no significant differences in OS and iPFS, which suggested that the number of BMs is an important factor in selecting the type of RT. Currently, several ongoing prospective trials are comparing SRS *vs.* WBRT for multiple BMs. For example, there is a phase III trial evaluating the OS in patients with 5–15 BM who received SRS compared with those who received hippocampal-avoidant WBRT plus memantine (NCT03550391). Other prospective trials are evaluating the differences in adverse effects of WBRT and SRS in patients with multiple BMs (NCT0192968; NCT 03075072). The results from these trials may help clinicians to select an optimal RT combination strategy.

We showed that pure chemotherapy has limited efficacy for BM. In contrast, a superior icORR and OS were observed in patients with BM treated with chemotherapy plus RT. Therefore, this therapy may be effective for non-targeted NSCLC patients with BM and a PD-L1-negative status. In addition, patients treated with chemotherapy plus bevacizumab had higher icORRs than patients treated with pure ICI, which may be explained by the fact that most patients in this subgroup received first-line treatment. The subgroup analysis confirmed this opinion.

Our study has several notable limitations. Most of the included studies were retrospective trials with small sample sizes, which could have resulted in selection bias. Furthermore, tumor response was not stratified according to certain inevitable influencing factors, such as the number and size of metastases. Further clinical trials are warranted to evaluate the efficacy of ICI-combined therapies and guide optimal clinical decisions.

Conclusions

For advanced non-targeted therapy NSCLC patients with BM, the current evidence suggests that the good clinical intracranial efficacy of ICI-based therapies, whether ICI plus chemotherapy or ICI plus RT, provides an impressive icORR and long-term survival benefits. In particular, patients who received first-line treatment or were PD-L1-positive could benefit more from ICI-based therapies, which leads to an improved icORR and prolonged survival. Moreover, chemotherapy plus RT had better efficacy for BM in patients with a PD-L1-negative status. The impacts of timing and technique on intracranial disease control need to be further validated in prospective trials. Currently, several ongoing trials are investigating the efficacy and safety of different treatments in advanced patients with baseline BM.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-515/rc

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-515/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-515/coif). TL serves as an unpaid Associate Editor-in-Chief of *Translational Lung Cancer Research* from November 2017 to November 2023. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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