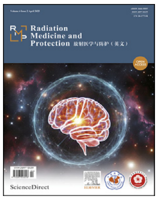
Radiation Medicine and Protection 6 (2025) 91–102

Contents lists available at ScienceDirect

Radiation Medicine and Protection

journal homepage: www.radmp.org



Original article

Survival benefits and toxicity effects of radiotherapy and immunotherapy treatments in melanoma patients with brain metastases: A meta-analysis

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ARTICLE INFO

Managing Editor: Chen Li

Keywords:
Immunotherapy
Radiotherapy
Melanoma brain metastases
Meta-analysis

ABSTRACT

Objective: To compare the efficacy and toxicity of four treatment strategies in patients with MBMs.
Methods: A systematic literature search of the Cochrane, PubMed, Embase, Web of Science, and OVID Medline databases was performed until July 24, 2024. A total of four therapeutic modalities for MBMs, including immune checkpoint inhibitor (ICI) monotherapy, radiotherapy (RT) alone, ICI combined with RT (ICI + RT), and dual ICI therapy (ICI + ICI), were evaluated by the overall survival (OS), intracranial progression-free survival (iPFS), and adverse effect (AE). The meta-analysis was performed using R language and registered in PROSPERO (registration no. CRD42023480912).
Results: This study included 33 studies comprising 2,496 patients with MBMs. ICI combined with RT and dual ICI therapy improved the 6 and 12-month OS rates compared with ICI monotherapy and RT alone. There was no significant difference in OS between the ICI + RT group and the ICI + ICI group. Similar results were observed for iPFS, with the combination treatment groups showing a significant difference compared with the treatment groups alone. However, no significant difference was observed in 1-year iPFS between the ICI + RT group and the ICI + ICI group ($P = 0.07$), whereas the ICI + ICI group demonstrated superior 2-year iPFS compared with the ICI + RT group ($P < 0.05$). Furthermore, the survival advantages of combination therapy gradually decreased with increasing duration of treatment. Additionally, compared with ICI monotherapy, dual ICI therapy significantly increased the incidence of AEs over grade 3 (ICI + ICI: 57% *vs.* ICI: 11%, $P < 0.0001$), whereas ICI combined with RT did not significantly differ (ICI + RT: 19% *vs.* ICI: 11%, $P = 0.14$).
Conclusion: The combination of ICI with RT offers superior survival benefits without increasing toxicity in patients with MBMs. However, this survival benefit decreases over time, and further optimizing the treatment strategy is essential for improving the outcomes of patients with MBMs.

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https://doi.org/10.1016/j.radmp.2025.02.001
Received 8 June 2024; Received in revised form 20 December 2024; Accepted 9 February 2025

1. Introduction

Melanoma is the deadliest form of skin cancer, and its incidence continues to increase globally, with the age-standardized incidence of melanoma estimated to be 0.9 per 100,000 people in China.[1,2] Brain metastases are common in advanced melanoma, with 75% of patients with metastatic melanoma developing brain metastases during disease progression.[3,4] However, the treatment of melanoma brain metastases (MBMs) remains a challenge, as the median survival time for these patients is only approximately four months.[4,5] Due to the exclusion of patients with newly diagnosed or symptomatic MBMs from many clinical trials, there is currently a lack of data to effectively guide the treatment of MBMs. Considering the poor outcomes for patients with MBMs, it is imperative to explore more effective treatment strategies to improve survival.

With advances in medical technology, several adjuvant treatments, including whole-brain radiation therapy (WBRT) and stereotactic radiation surgery (SRS), have been used to treat brain metastases. However, improvements in these treatments have been limited.[6–9] Recently, the advent of small-molecule targeted drugs and immunotherapy has significantly improved the therapeutic efficacy of MBMs treatment.[5,10–12] Among these modalities, immune checkpoint inhibitors (ICIs) have garnered widespread attention with their effectiveness in treating various soft tissue malignancies, including melanoma and non-small cell lung cancer.[13–15] Several studies have reported that ICIs can improve the survival of patients with advanced melanoma and even those with MBMs.[16–18] Michele et al.[19] reported that compared with patients who initially received placebo plus dacarbazine, twice as many patients who received ipilimumab plus dacarbazine survived for five years. Dual ICI therapy (a combination of two immune checkpoint inhibitors, namely, anti-PD1 and anti-CTLA4), has been clinically applied with better long-term efficacy than a single ICI in advanced melanoma.[20,21] Additionally, some studies have demonstrated a long-lasting survival benefit with the combination of ICI and RT in advanced melanoma patients.[22–24] However, for patients with MBMs, both of the aforementioned combination therapies are challenging to achieve long-term overall survival (OS).

Although ICIs have expanded the therapeutic window and provided new treatment options for patients with MBMs, treatment strategies for MBMs remain controversial, due to no established guidelines or comprehensive randomized controlled trials comparing different treatments. Thus, it is crucial to conduct in-depth comparisons of various treatment regimens to determine which is more appropriate for patients with MBMs. Therefore, we conducted this study to compare the efficacy of four treatment strategies in patients with MBMs: ICI monotherapy, RT, dual ICI therapy, and ICI combined with RT. This study aims to provide valuable insights by assessing the survival benefits and toxicity of four different treatment strategies through indirect comparisons, offering important guidance for clinical decision making.

2. Materials and methods

2.1. Search strategy and eligibility criteria

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was duly registered in PROSPERO under registration number CRD42023480912. A literature search for relevant articles published in the last twenty years was conducted using the Cochrane, PubMed, Embase, Web of Science, and OVID databases until July 24, 2024. A systematic literature search was executed utilizing “melanoma,” “radiotherapy or immune checkpoint inhibitors” and “brain metastases” as indexed search terms, complemented by MeSH-derived terminology, to identify relevant articles in several of the above databases. The types of articles included were limited to clinical trials and randomized controlled trials.

After removing duplicate articles, two reviewers independently evaluated the titles and abstracts to ensure the relevance of the articles. The following eligibility criteria were established for article selection: 1) clinical trials evaluating the survival benefit or toxicity of treatments involving ICI or RT in patients with MBMs (if a trial also included other tumor types, the article was considered qualified if survival data on patients with MBMs could be retrieved); 2) articles were considered qualified if they provided sufficient information and data to obtain OS, intracranial progression-free survival (iPFS), or adverse effects (AEs) for each treatment strategy; and 3) priority was given to studies on asymptomatic MBMs patients without prior local brain therapy or those who had received at least three months of systemic therapy. In addition, we excluded studies that met any of the following criteria: 1) review; 2) case report or case series with fewer than 10 cases; 3) conference abstract; 4) letter, editorial, comment, note, short survey, or book chapter; 5) article not within the field of interest; or 6) phase I clinical trial or preclinical research. Following the initial screening, all the manuscripts that met the criteria were reviewed for further confirmation. The exclusion criteria for the second screening were as follows: 1) studies that did not report any outcomes, including OS, iPFS, or AE; 2) studies in which data for the MBMs could not be identified or isolated; 3) studies from which data could not be extracted; 4) studies with a partially overlapping patient cohort; or 5) studies in which data for the treatment strategies of interest could not be identified or isolated.

2.2. Data extraction and quality assessment

After the literature screening, the following information was extracted from the final selected studies using a standardized extraction form: 1) study characteristics, including author, publication year, and study type; 2) treatment-related information, including treatment group, ICI used, and RT type; 3) baseline patient characteristics, including number of patients, male–female ratio, number of *BRAF V600* mutations, Karnofsky (KPS) and Eastern Cooperative Oncology Group Performance Status (ECOG PS); and 4) characteristics associated with endpoints, including median OS, OS rates at 6, 12, 18, and 24 months, median iPFS, iPFS rates at 1 and 2 years, and AEs. For some cohort studies, we extracted data only for the cohort of asymptomatic MBMs patients who had not previously received local brain therapy, in order to exclude the effects of prior brain therapy on efficacy and toxicity. For studies where raw survival data were unavailable, data were identified and extracted via Engauge Digitizer software (GitHub, version 11.1). The risk of bias and quality of the studies were assessed using different risk of bias assessment tools. The quality of the included randomized controlled studies and the non-randomized controlled studies was assessed using the Cochrane risk-of-bias tool ROB 2.0 and ROBINS-I.[25,26] For the assessment of the single cohort studies, the Methodological Index for Non-Randomized Studies (MINORS) tool was used.[27]

2.3. Statistical analysis

The meta-analysis of pooled results was conducted using the inverse variance method to calculate weights, with the DerSimonian–Laird random effects model employed to determine pooled estimates and 95% confidence intervals (*CIs*). Heterogeneity between studies was assessed using the I^2 statistic, with an $I^2 > 50\%$ indicating the presence of heterogeneity. Publication bias was evaluated using funnel plots and Egger's and Begg's tests. Additionally, to test whether the individual treatment groups had significant effects in the meta-regressions, we employed the *Wald*-type *Chi*-square test with adjustment for multiplicity. We used the obtained regression coefficients to estimate the intervention effect and the odds ratio (*OR*) for the reference group. Sensitivity analyses were conducted for all studies to identify the sources of heterogeneity. Statistical analyses were performed with R software (version 4.2.2).

3. Results

3.1. Literature search

The literature selection process is shown in Fig. 1. A total of 726 references were identified from the five databases and an additional manual search. Additionally, 202 duplicate studies were removed. A total of 453 articles were excluded after reviewing their titles and abstracts, with specific details as follows: 1) review ($n = 109$); 2) case report or case series with fewer than 10 cases ($n = 4$); 3) conference abstract ($n = 163$); 4) letter, editorial, comment, note, short survey or chapter ($n = 9$); 5) article not in the field of interest ($n = 155$); and 6) phase I trial or preclinical research ($n = 13$). Subsequently, 19 articles were excluded due to lack of access to the full text and 52 potentially eligible articles were assessed according to the inclusion and exclusion criteria, and 19 articles were excluded for the following reasons: 1) no reporting any outcome, including OS, iPFS or AE ($n = 7$); 2) data for the melanoma brain metastases that could not be identified or isolated ($n = 5$); 3) data could not be extracted ($n = 4$); 4) studies with partially overlapping patient cohorts ($n = 1$); and 5) data for the treatment strategies of interest that could not be identified or isolated ($n = 2$). Finally, 33 articles that met the inclusion criteria were included.

3.2. Study characteristics

The characteristics of the studies are shown in Table 1. Among the 33 studies, 6 were phase II clinical trials,[18,28–32] 2 were phase III clinical trials,[33,34] and the rest were retrospective studies.[35–59] Additionally, 14 of the 33 studies had multiple cohorts.[18,28,31,35–37,41,43,44,48,50,51,53,54] Among the 33 included studies, 9 studies involved dual ICI therapy strategies,[28,29,31,33,34,52–55] 17 studies involved ICIs combined with RT,[35–51] 10 studies involved RT alone,[35–37,41,43,51,57,59–61] and 6 studies involved ICI monotherapy among the 33 included studies.[18,28,30,32,54,56] To unify the studies into single-arm studies, the 14 multicohort studies were divided into several single cohort studies, and those single cohorts meeting the inclusion criteria were included in the study.

3.3. Quality assessment

Data for the quality assessment of randomized controlled studies based on the ROB 2 tool and for the non-randomized controlled studies based on the ROBINS-I tool were shown in Supplementary Figures S1 and S2, respectively. Three randomized controlled studies included were evaluated via the ROB 2 tool,[28,31,33] two were considered to have a moderate risk[28,33] and one was considered high risk due to bias arising from the randomization process.[31] Following the quality assessment of the sixteen included studies according to the ROBINS-I tool,[18,22,34,36,37,40,41,43,44,48,50–55] ten studies had a moderate risk of bias,[34,35,37,40,41,44,48,50,52,55] and the remaining six studies were considered to have a severe risk of bias.[18,36,43,51,53,54] Among the six studies identified as having a risk of severe bias, four were identified as having a high risk of confounding bias,[18,36,51,53] one was identified as having a missing data bias,[43] and one was identified as having a risk of severe bias due to a bias in outcome measures.[54] Additionally, fourteen single-arm studies were evaluated via MINORS tools,[29,30,38,39,42,45–47,49,56–60] and all scored above 10 points. The quality assessment of the single-arm cohort studies based on the MINORS scale are presented in Supplementary Table 1.

3.4. Effects of ICI + ICI, ICI + RT, RT and ICI on general OS

A total of 23 studies involving 27 cohorts and 1,962 patients were analyzed for short-term OS. The effects of different treatment strategies on the 6-month OS of patients with MBMs were shown in Fig. 2. The pooled 6-month OS rates, based on the random effects model, were 89% (95% *CI*, 83%–94%; $I^2 = 37\%$), 84% (95% *CI*, 78%–89%; $I^2 = 48\%$), 52% (95% *CI*, 46%–57%; $I^2 = 49\%$), and 44% (95% *CI*, 35%–53%; $I^2 = 19\%$) for ICI combined with RT, dual ICI therapy, RT alone, and ICI monotherapy, respectively. Among the 23 included studies that investigated patients who received dual ICI therapy, the 12-month OS rate was 67% (95% *CI*, 61%–72%; $I^2 = 16\%$). The 12-month OS rate of patients treated with ICI combined with RT was 66% (95% *CI*, 61%–71%; $I^2 = 0$), while for those treated with RT alone or ICI monotherapy, it was 25% (95 % *CI*,

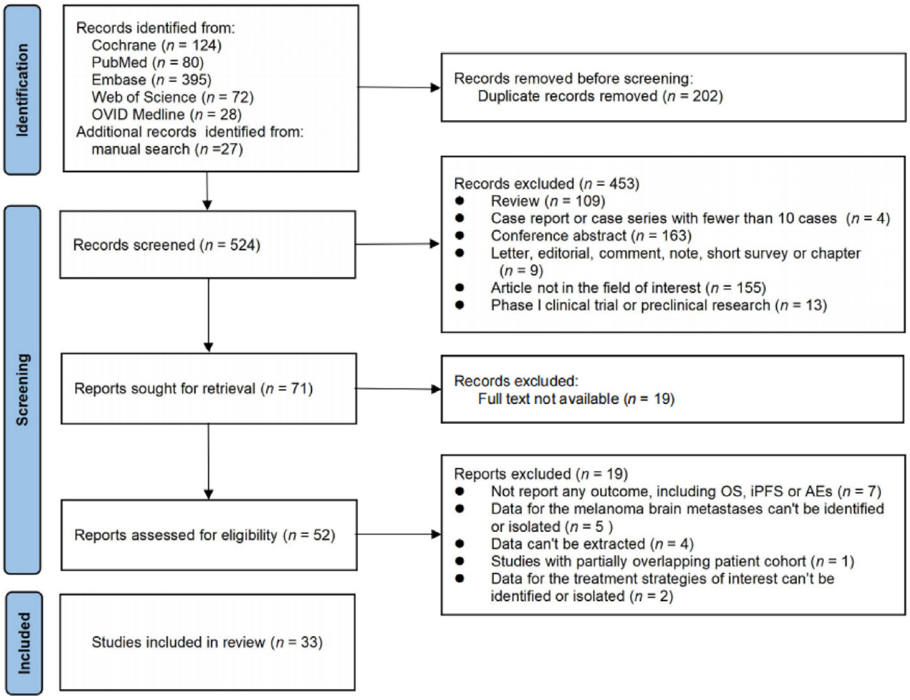


Fig. 1. Flow diagram of the study selection process for radiotherapy and immunotherapy treatments in MBM.

Table 1
Characteristics of the included studies.

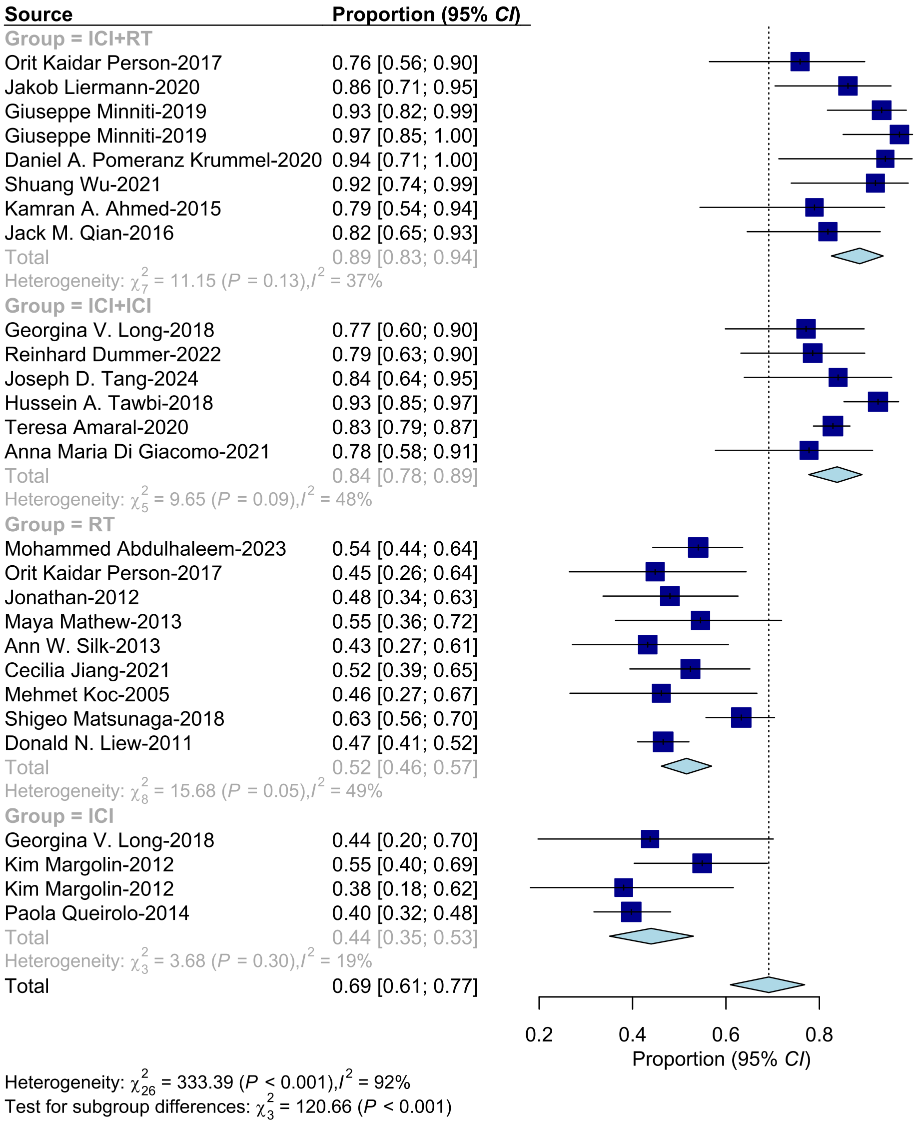
Ref.	Year	Study Type	Group	ICI Used	Radiotherapy	Patient Number	Age	Male	Female	BRAF V600 Mutation	KPS	ECOG PS	
												0–1	≥2
35	2012	retrospective	ICI + RT	Ipilimumab	SRS	27	53.2	16	11	-	-	15	2
36	2013	retrospective	ICI + RT	Ipilimumab	SRS	25	62	13	12	-	90	-	-
37	2013	retrospective	ICI + RT	Ipilimumab	SRS/WBRT	33	56.6	20	13	13	-	27	1
38	2015	retrospective	ICI + RT	Ipilimumab	SRS	13	64	7	6	-	-	-	-
39	2015	retrospective	ICI + RT	Anti-PD1	SRS	19	-	-	-	-	-	-	-
40	2016	retrospective	ICI + RT	Anti-PD1/Anti-CTLA4	SRS	33	64.1	24	9	10	90	-	-
41	2017	retrospective	ICI + RT	Ipilimumab/ Pembrolizumab/Nivolumab	FSRT/SRS	29	57	-	-	13	90	-	-
42	2017	retrospective	ICI + RT	Pembrolizuma	SRS	21	67	14	7	5	-	-	-
43	2018	retrospective	ICI + RT	Pembrolizumab/Nivolumab	SRS	13	52	6	7	8	-	-	-
44	2019	retrospective	ICI + RT	Ipilimumab	SRS	45	54	28	17	15	80	-	-
44	2019	retrospective	ICI + RT	Nivolumab	SRS	35	56	21	14	13	80	-	-
45	2020	retrospective	ICI + RT	UK	SRS/WBRT	17	54	13	4	5	-	-	-
46	2020	retrospective	ICI + RT	Anti-PD1	SRS	50	66	30	20	29	-	42	8
47	2020	retrospective	ICI + RT	Ipilimumab/Nivolumab	SRS	36	63	28	8	14	-	-	-
48	2020	retrospective	ICI + RT	Ipilimumab	SRS	10	67.3	8	2	-	-	9	1
48	2020	retrospective	ICI + RT	Anti-PD1	SRS	9	62.1	5	4	-	-	6	3
49	2021	retrospective	ICI + RT	Anti-PD1	SBRT/SRS/ WBRT	25	48	12	13	11	-	-	-
50	2021	retrospective	ICI + RT	Ipilimumab	SRT/SRS	53	59.7	27	26	21	-	53	0
51	2023	retrospective	ICI + RT	Pembrolizumab/ Ipilimumab/Nivolumab	–	24	62.2	13	11	-	-	-	-
28	2018	phase II	ICI + ICI	Ipilimumab + Nivolumab	–	35	59	29	6	19	-	34	1
29	2018	phase II	ICI + ICI	Ipilimumab + Nivolumab	–	94	59	65	29	-	-	-	-
52	2020	retrospective	ICI + ICI	Ipilimumab + Nivolumab	–	380	-	240	140	138	-	336	39
33	2021	phase III	ICI + ICI	Ipilimumab + Nivolumab	–	27	56	17	10	11	-	27	0
31	2021	phase II	ICI + ICI	Ipilimumab + Nivolumab	–	101	59	68	33	66	-	-	-
53	2021	retrospective	ICI + ICI	Ipilimumab + Nivolumab	–	17	-	-	-	-	-	-	-
54	2022	retrospective	ICI + ICI	Ipilimumab + Nivolumab	–	29	-	-	-	-	-	-	-
34	2022	phase III	ICI + ICI	Ipilimumab + Nivolumab	–	42	54.5	31	11	18	-	35	7
55	2024	retrospective	ICI + ICI	Ipilimumab + Nivolumab	–	25	64	16	9	-	-	-	-
18	2012	phase II	ICI	Ipilimumab	–	51	59	33	18	-	-	51	0
18	2012	phase II	ICI	Ipilimumab	–	21	57	11	10	-	-	21	0
56	2014	retrospective	ICI	Ipilimumab	–	146	54	76	70	-	-	-	-
32	2016	phase II	ICI	Pembrolizumab	–	18	65	12	6	6	-	-	-
30	2018	phase II	ICI	Pembrolizuma	–	23	65	15	8	9	-	23	0
28	2018	phase II	ICI	Nivolumab	–	25	63	19	6	14	-	25	0
28	2018	phase II	ICI	Nivolumab	–	16	51	11	5	13	-	15	1
54	2022	retrospective	ICI	Pembrolizumab/Nivolumab	–	43	-	-	-	-	-	-	-
54	2022	retrospective	ICI	Ipilimumab	–	14	-	-	-	-	-	-	-
57	2005	retrospective	RT	–	SRS	26	52.7	15	11	-	-	-	-
60	2011	retrospective	RT	–	SRS	333	-	224	109	-	-	-	-
35	2012	retrospective	RT	–	SRS	50	59.3	33	17	-	-	45	5
37	2013	retrospective	RT	–	SRS/WBRT	37	57.7	20	17	1	-	28	7
36	2013	retrospective	RT	–	SRS	33	57	17	16	-	90	-	-
41	2017	retrospective	RT	–	FSRT/SRS	29	62	-	-	3	90	-	-
43	2018	retrospective	RT	–	SRS	13	64	8	5	10	-	-	-
58	2018	retrospective	RT	–	SRS	177	66	105	72	-	90	-	-
59	2021	retrospective	RT	–	WBRT	63	54.2	39	24	8	-	47	16
51	2023	retrospective	RT	–	SRS	111	57.8	75	36	-	-	-	-

Note: -, no data; RT, radiotherapy; ICI, immune checkpoint inhibitor; WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery; FSRT, fractionated stereotactic radiotherapy; SBRT, stereotactic body radiotherapy.

22%–28%; $I^2 = 0$) or 24% (95% *CI*, 16%–31%; $I^2 = 15\%$), respectively, as shown in Fig. 3. The distribution of Deeks funnel plot results was relatively uniform, as shown in Figure S3, and no significant publication bias was detected according to Egger's test or Begg's test results, with details described in Supplementary Figures S4 and S5.

The meta-regression results for the 6-month and 12-month OS rates are shown in Tables 2 and 3. The meta-regression analysis revealed a significant difference in OS between the ICI + RT group and the non-combination therapy group (ICI group or RT group). However, no significant difference was found between the ICI + RT group and the ICI + ICI group. In other words, ICI combined with RT did not provide a significantly greater survival benefit for patients with MBMs than dual ICI therapy. Nonetheless, combination therapy (ICI + RT, ICI + ICI) was associated with a greater short-term OS rate in MBMs patients than ICI monotherapy or RT alone.

To assess whether the four treatment strategies were beneficial in terms of mid-term survival outcomes, data from 33 studies were extracted to evaluate the effect of treatment regimens on OS at different time points (6, 12, 18, and 24 months), as shown in Fig. 4. Compared with any single treatment, combination therapies resulted in significant improvements at short-term time points. However, the effects of the two combination therapies on maintaining patient survival were similar. While survival outcomes for patients receiving ICI combined with RT were better than single treatment, this benefit declined after 18 months. Additionally, compared with the other three treatments, dual ICI therapy demonstrated lasting efficacy in increasing patient survival rates, both in



Source	Proportion (95% *CI*)
Group = ICI+RT	
Orit Kaidar Person-2017	0.76 [0.56; 0.90]
Jakob Liermann-2020	0.86 [0.71; 0.95]
Giuseppe Minniti-2019	0.93 [0.82; 0.99]
Giuseppe Minniti-2019	0.97 [0.85; 1.00]
Daniel A. Pomeranz Krummel-2020	0.94 [0.71; 1.00]
Shuang Wu-2021	0.92 [0.74; 0.99]
Kamran A. Ahmed-2015	0.79 [0.54; 0.94]
Jack M. Qian-2016	0.82 [0.65; 0.93]
Total	0.89 [0.83; 0.94]
Heterogeneity: $\chi^2_7 = 11.15$ ($P = 0.13$), $I^2 = 37\%$	
Group = ICI+ICI	
Georgina V. Long-2018	0.77 [0.60; 0.90]
Reinhard Dummer-2022	0.79 [0.63; 0.90]
Joseph D. Tang-2024	0.84 [0.64; 0.95]
Hussein A. Tawbi-2018	0.93 [0.85; 0.97]
Teresa Amaral-2020	0.83 [0.79; 0.87]
Anna Maria Di Giacomo-2021	0.78 [0.58; 0.91]
Total	0.84 [0.78; 0.89]
Heterogeneity: $\chi^2_5 = 9.65$ ($P = 0.09$), $I^2 = 48\%$	
Group = RT	
Mohammed Abdulhaleem-2023	0.54 [0.44; 0.64]
Orit Kaidar Person-2017	0.45 [0.26; 0.64]
Jonathan-2012	0.48 [0.34; 0.63]
Maya Mathew-2013	0.55 [0.36; 0.72]
Ann W. Silk-2013	0.43 [0.27; 0.61]
Cecilia Jiang-2021	0.52 [0.39; 0.65]
Mehmet Koc-2005	0.46 [0.27; 0.67]
Shigeo Matsunaga-2018	0.63 [0.56; 0.70]
Donald N. Liew-2011	0.47 [0.41; 0.52]
Total	0.52 [0.46; 0.57]
Heterogeneity: $\chi^2_8 = 15.68$ ($P = 0.05$), $I^2 = 49\%$	
Group = ICI	
Georgina V. Long-2018	0.44 [0.20; 0.70]
Kim Margolin-2012	0.55 [0.40; 0.69]
Kim Margolin-2012	0.38 [0.18; 0.62]
Paola Queirolo-2014	0.40 [0.32; 0.48]
Total	0.44 [0.35; 0.53]
Heterogeneity: $\chi^2_3 = 3.68$ ($P = 0.30$), $I^2 = 19\%$	
Total	0.69 [0.61; 0.77]

Heterogeneity: $\chi^2_{26} = 333.39$ ($P < 0.001$), $I^2 = 92\%$
Test for subgroup differences: $\chi^2_3 = 120.66$ ($P < 0.001$)

Fig. 2. Pooled analysis of the 6-month OS rate of patients with brain metastases from melanoma under four treatment modalities (ICI + RT, ICI + ICI, RT, and ICI). Note: RT. radiotherapy; ICI. Immune checkpoint inhibitor; *CI*. confidence interval; χ^2. Chi-square test, subscripts were degrees of freedom.

the short term and the mid term.

3.5. *Effects of ICI + ICI, ICI + RT, RT and ICI on iPFS*

The iPFS within 2 years was comprehensively reported in 13 studies, including 4 with ICI + RT, 5 with ICI + ICI, 2 with RT and 3 with ICI. The pooled 1-year iPFS rates, based on random effects modeling, were 48% (95% *CI*, 40%–56%; $I^2 = 7\%$), 57% (95% *CI*, 52%–63%; $I^2 = 0$), 32% (95% *CI*, 21%–44%; $I^2 = 33\%$), and 5% (95% *CI*, 0–14%; $I^2 = 45\%$) when ICI + RT, ICI + ICI, ICI and RT were used, respectively, as shown in Fig. 5. Additionally, the 2-year iPFS rate of patients treated with ICI combined with RT was 39% (95% *CI*, 30%–49%; $I^2 = 18\%$), whereas the iPFS rate for patients treated with dual ICI therapy was 52% (95% *CI*, 47%–58%; $I^2 = 0$), and those of patients treated with RT alone or ICI monotherapy were 2% (95% *CI*, 0–6%; $I^2 = 0$) or 27% (95% *CI*, 19%–36%; $I^2 = 10\%$) (Fig. 6), respectively. The distribution of Deeks funnel plot results was relatively uniform, as shown in Figure S6, and no significant publication bias was detected according to Egger's test or Begg's test results, with details described in Supplementary Figures S7 and S8.

The meta-regression results for 1-year and 2-year iPFS are shown in Tables 4 and 5. The meta-regression analysis revealed that the difference in iPFS between the combination therapy groups (ICI + RT, ICI + ICI) and the non-combination therapy groups (ICI or RT) was significant, whereas no significant difference was found between the ICI + RT group and the ICI + ICI group at 1-year iPFS rate ($P = 0.07$). However, the ICI + ICI group had a significantly higher 2-year iPFS rate compared to the ICI + RT group ($P < 0.05$). Patients treated with ICI had a significantly higher iPFS rate than did those treated with RT. In summary, combination therapy (ICI + RT, ICI + ICI) effectively improved the iPFS compared with any single treatment (RT, ICI), while ICI treatment led to better iPFS than RT.

3.6. *Comparison of the toxicities of ICI + ICI, ICI + RT, RT and ICI*

The AEs for each treatment arm were summarized, including the incidence of AEs and grade 3 or higher AEs. The pooled AE rates were 80% (95% *CI*, 63%–93%; $I^2 = 69\%$), 92% (95% *CI*, 85%–98%; $I^2 = 71\%$), 55% (95% *CI*, 44%–67%; $I^2 = 0$), and 63% (95% *CI*, 52%–73%; $I^2 = 36\%$) for ICI + RT, ICI + ICI, RT alone, and ICI monotherapy, respectively, as shown in Figure S9. Additionally, subgroup analyses based on the grade of AEs were performed, and severe AEs were further concerned, as shown in Fig. 7. The pooled grade 3 or 4 AE rates were 19% (95% *CI*, 11%–28%;

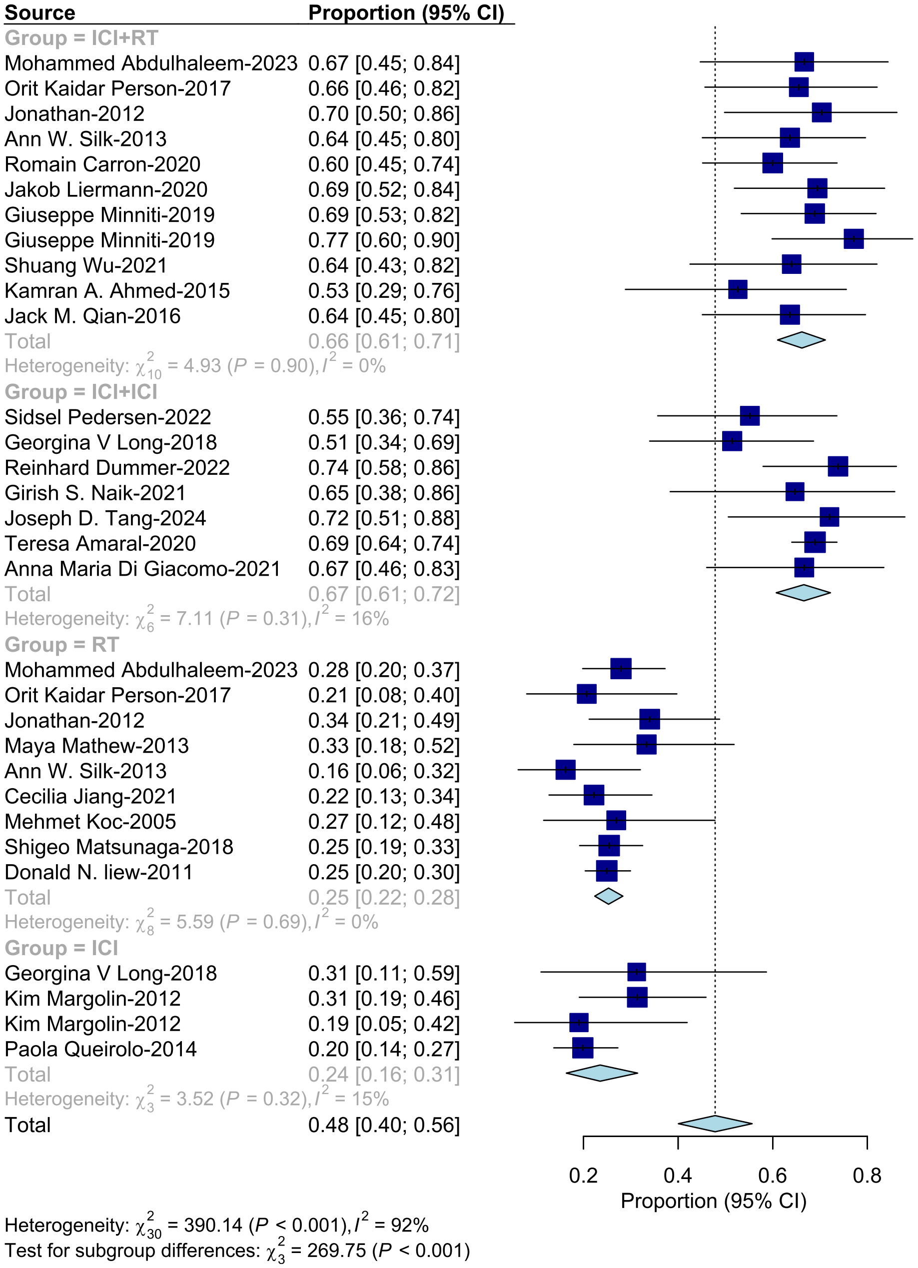


Fig. 3. Pooled analysis of the 12-month OS rate of patients with brain metastases from melanoma under four treatment modalities (ICI + RT, ICI + ICI, RT, and ICI). Note: RT. radiotherapy; ICI. Immune checkpoint inhibitor; *CI.* confidence interval; χ^2. Chi-square test, subscripts were degrees of freedom.

Table 2
Meta-regression summary of 6-month overall survival.

Subtype	RT		ICI		ICI + RT		ICI + ICI	
	OR(95% *CI*)	*P*-value	*OR*(95% *CI*)	*P*-value	*OR*(95% *CI*)	*P*-value	*OR*(95% *CI*)	*P*-value
RT	1	–	0.930	0.191	1.503	<0.0001	1.416	<0.0001
ICI	1.075	0.191	1	–	1.616	<0.0001	1.522	<0.0001
ICI + ICI	0.706	<0.0001	0.657	<0.0001	1.062	0.253	1	–
ICI + RT	0.665	<0.0001	0.619	<0.0001	1	–	0.942	0.253

Note: –, no data; RT, radiotherapy; ICI, immune checkpoint inhibitor.

Table 3
Meta-regression summary of 12-month overall survival.

Subtype	RT		ICI		ICI + RT		ICI + ICI	
	OR (95% *CI*)	*P*-value	*OR* (95% *CI*)	*P*-value	*OR* (95% *CI*)	*P*-value	*OR* (95% *CI*)	*P*-value
RT	1	–	0.972	0.435	1.510	<0.0001	1.536	<0.0001
ICI	1.029	0.435	1	–	1.554	<0.0001	1.581	<0.0001
ICI + RT	0.662	<0.0001	0.644	<0.0001	1	–	1.017	0.610
ICI + ICI	0.651	<0.0001	0.633	<0.0001	0.983	0.610	1	–

Note: –, no data; RT, radiotherapy; ICI, immune checkpoint inhibitor.

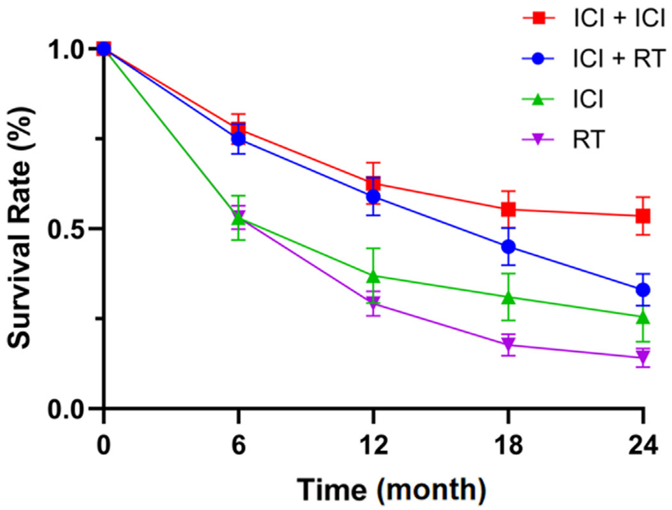


Fig. 4. Pooled overall survival by type of treatment for each time point. ICI + ICI indicates a combination of 2 immune checkpoint inhibitors; ICI + RT indicates an immune checkpoint inhibitor combined with radiotherapy; RT indicates radiotherapy; ICI indicates immune checkpoint inhibitor monotherapy.

$I^2 = 0$), 57% (95% *CI*, 52%–63%; $I^2 = 0$), and 11% (95% *CI*, 6%–17%; $I^2 = 0$) for ICI + RT, ICI + ICI, and ICI monotherapy. The meta-regression results revealed that dual ICI therapy significantly increased the incidence of AEs above grade 3 compared to ICI alone (ICI + ICI: 57% *vs.* ICI: 11%, $P < 0.0001$), whereas ICI combined with RT did not significantly affect this difference (ICI + RT: 19% *vs.* ICI: 11%, $P = 0.14$), as shown in Table 6. The distribution of Deeks funnel plot results was relatively uniform, as shown in Figure S10, and no significant publication bias was detected according to Egger's test or Begg's test results, with details described in Supplementary Figures S11 and S12. To exclude the influence of specific studies on the effect size, sensitivity analysis was performed, which revealed that the meta-analysis results were stable, as detailed in the Supplementary Table S7.

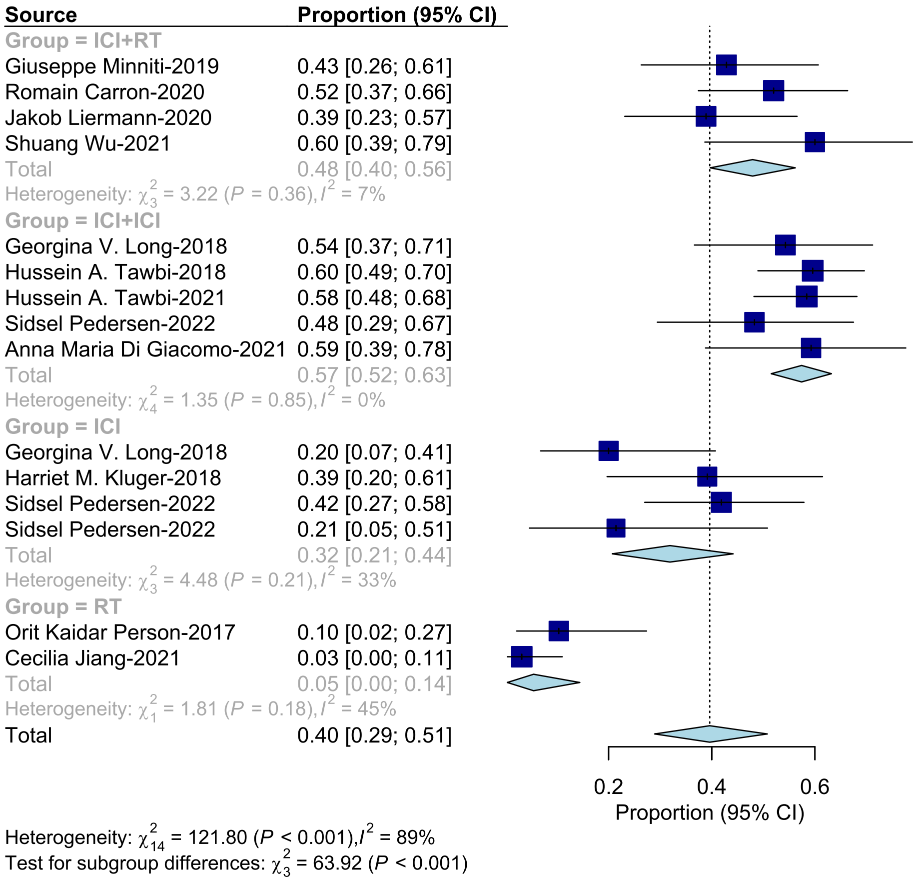
4. Discussion

In recent years, immunotherapy has garnered significant attention because of its efficacy in a variety of solid tumors. The most representative form of immunotherapy is "ICItherapy", developed from the "important target of immunotherapy"[62,63] discovered by Tasuku Honjo and James P. Allison. ICIs are commonly used in patients with MBMs either as a single strategy or in combination with local regional therapy (radiotherapy, RT). Currently, treatments for MBMs, including immunotherapy and RT, have been approved for clinical use; however, their efficacy and toxicity effects remain a subject of debate. To clarify these issues, several meta-analyses have been conducted. For example, a previous meta-analysis revealed that intracranial objective response rates (ORRs) and disease control rates (DCRs) were significantly higher with combination therapy compared to ICI monotherapy, but survival-related outcomes in MBMs patients have not been reported.[64] The impact of different therapies on OS in MBMs patients remains unclear. Another study evaluated MBMs treatments, including stereotactic radiotherapy combined with immunotherapy (SRS + IT), through direct and indirect comparisons. This study revealed that SRS + IT was superior to IT or SRS alone in improving intracranial function, particularly progression-free survival (PFS) and OS.[65] However, the survival benefits of this treatment strategy vary at different time points. A comprehensive analysis of the therapeutic effects of various strategies over time is necessary.

This meta-analysis revealed that combination therapy, including ICI + RT and ICI + ICI, was associated with greater short-term OS (6 months, 12 months) rates in patients with MBMs than either single therapy, including RT alone or ICI monotherapy. There was no significant difference in OS between the ICI + RT and ICI + ICI groups. Importantly, the survival advantage of combination therapy (ICI + RT or ICI + ICI) may be limited in the short term, and the difference in OS between combination therapy and single treatments has decreased over time. Compared with the other three treatments, dual ICI therapy demonstrated superior efficacy in improving patient OS rates, both in the short and mid term. Similarly, combination therapy (ICI + RT, ICI + ICI) effectively improved the iPFS for patients with MBMs compared with single treatment. In terms of toxicity, the ICI + ICI intervention significantly increased the occurrence of AEs, including AEs over grade 3, in patients, whereas no statistically significant difference was detected between ICI + RT and ICI monotherapy. In summary, combination therapy (ICI + RT, ICI + ICI) offered superior survival benefits in patients with MBMs compared with the other three treatment strategies. Importantly, ICI combined with RT provides survival benefits without increasing toxicity, although this survival benefit decreases over time. Compared with other treatment strategies, dual ICI therapy demonstrated a sustained effect on increasing patient survival rates in both the short and mid term, though the accompanying incidence of AEs was also significantly increased. Extending this advantage is crucial for improving outcomes in patients with MBMs.

Due to the presence of blood–brain barrier, macromolecular drugs such as ICIs are prevented from entering the brain, resulting in limited efficacy for patients with MBMs.[66] RT has been used to potentially enhance the efficacy of ICI monotherapy in the treatment of MBMs. Our study also revealed that ICI combined with RT offers better survival benefits and less toxicity. This synergistic effect of RT in combination with immunotherapy may be attributed to the fact that local radiation in the brain can create a brief void in the blood–brain barrier, allowing to the uptake of ICI.[67]

Furthermore, RT can potentially induce immunogenic cell death in tumor cells, releasing a series of immune-related molecular signals and stimulating a cytotoxic immune response. On this basis, the combination of RT with immunotherapy may enhance the systemic antitumor response and lead to an abscopal effect associated with prolonged survival.[68–70] Notably, the survival benefits from ICI + RT are significantly more pronounced in the short term but gradually decrease over time. The lack of lasting efficacy may be due to numerous factors. MBMs



Source	Proportion (95% CI)
Group = ICI+RT	
Giuseppe Minniti-2019	0.43 [0.26; 0.61]
Romain Carron-2020	0.52 [0.37; 0.66]
Jakob Liermann-2020	0.39 [0.23; 0.57]
Shuang Wu-2021	0.60 [0.39; 0.79]
Total	0.48 [0.40; 0.56]
Heterogeneity: $\chi^2_3 = 3.22$ ($P = 0.36$), $I^2 = 7\%$	
Group = ICI+ICI	
Georgina V. Long-2018	0.54 [0.37; 0.71]
Hussein A. Tawbi-2018	0.60 [0.49; 0.70]
Hussein A. Tawbi-2021	0.58 [0.48; 0.68]
Sidsel Pedersen-2022	0.48 [0.29; 0.67]
Anna Maria Di Giacomo-2021	0.59 [0.39; 0.78]
Total	0.57 [0.52; 0.63]
Heterogeneity: $\chi^2_4 = 1.35$ ($P = 0.85$), $I^2 = 0\%$	
Group = ICI	
Georgina V. Long-2018	0.20 [0.07; 0.41]
Harriet M. Kluger-2018	0.39 [0.20; 0.61]
Sidsel Pedersen-2022	0.42 [0.27; 0.58]
Sidsel Pedersen-2022	0.21 [0.05; 0.51]
Total	0.32 [0.21; 0.44]
Heterogeneity: $\chi^2_3 = 4.48$ ($P = 0.21$), $I^2 = 33\%$	
Group = RT	
Orit Kaidar Person-2017	0.10 [0.02; 0.27]
Cecilia Jiang-2021	0.03 [0.00; 0.11]
Total	0.05 [0.00; 0.14]
Heterogeneity: $\chi^2_1 = 1.81$ ($P = 0.18$), $I^2 = 45\%$	
Total	0.40 [0.29; 0.51]

Heterogeneity: $\chi^2_{14} = 121.80$ ($P < 0.001$), $I^2 = 89\%$
Test for subgroup differences: $\chi^2_3 = 63.92$ ($P < 0.001$)

Fig. 5. Pooled analysis of the 1-year iPFS rate of patients with brain metastases from melanoma under four treatment modalities (ICI + RT, ICI + ICI, RT, and ICI). Note: RT. radiotherapy; ICI. Immune checkpoint inhibitor; *CI.* confidence interval; χ^2. Chi-square test, subscripts were degrees of freedom.

may be associated with resistance mechanisms, including inadequate drug delivery and specific brain microenvironmental features, each of which may lead to changes in the expression of genetic drivers.[71]

As stated earlier, the presence of the blood–brain barrier may impair the efficacy of dual ICI therapy. However, dual ICI therapy, such as anti-CTLA-4 and anti-PD-1 therapies, can effectively block the binding of their corresponding receptors to their ligands, thereby promoting the immune response against tumors. Owing to the different but complementary roles of anti-CTLA-4 and anti-PD-1 in T-cell activation, combined blockade increases the infiltration of tumor-effector T cells and the ratio of effector T cells to myeloid-derived suppressor cells, as well as the number of CD8+ T cells that produce interferon (IFN)-γ and tumor necrosis factor (TNF)-α. These cells can enter brain and attack tumor cells in the metastases.[72] Although dual ICI therapy also resulted in better survival outcomes, this synergistic effect was accompanied by a significant increase in the incidence rate of AEs above grade 3. The augmented efficacy is associated with an increased risk of immune-related AEs, necessitating careful patient selection and vigilant management to ensure optimal therapeutic outcomes.

Improving efficacy without increasing toxicity may be the key to prolonging survival in MBMs patients. Owing to the presence of blood-brain barrier, macromolecular drugs often cannot penetrate the brain effectively, making it difficult to achieve therapeutic concentrations at the target site, which is one of the main factors limiting the survival of patients with MBMs.[71] Several new therapeutic strategies for MBMs have been developed. One such approach involves the development of small-molecule drugs that can successfully penetrate the brain, such as small-molecule targeted therapies. Currently, targeted therapies such as BRAF and MEK inhibitors, which are widely used to treat MBMs patients, have demonstrated significant efficacy. In addition, combinations of different treatment strategies, such as targeted therapy combined with immunotherapy, and RT combined with targeted therapy, are increasingly being applied to MBMs patients and have shown promising results. Nonetheless, it is crucial to acknowledge the diverse pathological characteristics of individual patients and tailor treatment strategies accordingly. Personalized treatment plans should be prioritized to enhance therapeutic efficacy while minimizing AEs. When evaluating combination drug strategies, it is essential to focus on developing a safe and effective approach that delivers optimal outcomes.

This meta-analysis has several notable limitations. First, it did not have access to detailed patient-level data, and all survival data were extracted from published papers rather than from various databases. Second, all survival analyses conducted in this meta-analysis used single-cohort data, and the differences in survival outcomes between various treatment strategies were based on indirect comparisons of combined effect sizes rather than direct comparisons. Last, since the analysis was based on indirect comparisons and no randomized controlled trials were included, most of studies were retrospective, it is necessary to conduct prospective trials to compare the survival efficacy of dual ICI therapy and ICI combined with RT. While the combination of ICI and RT has demonstrated excellent therapeutic effects in improving survival, the sustained effect was not long known, indicating that treatment

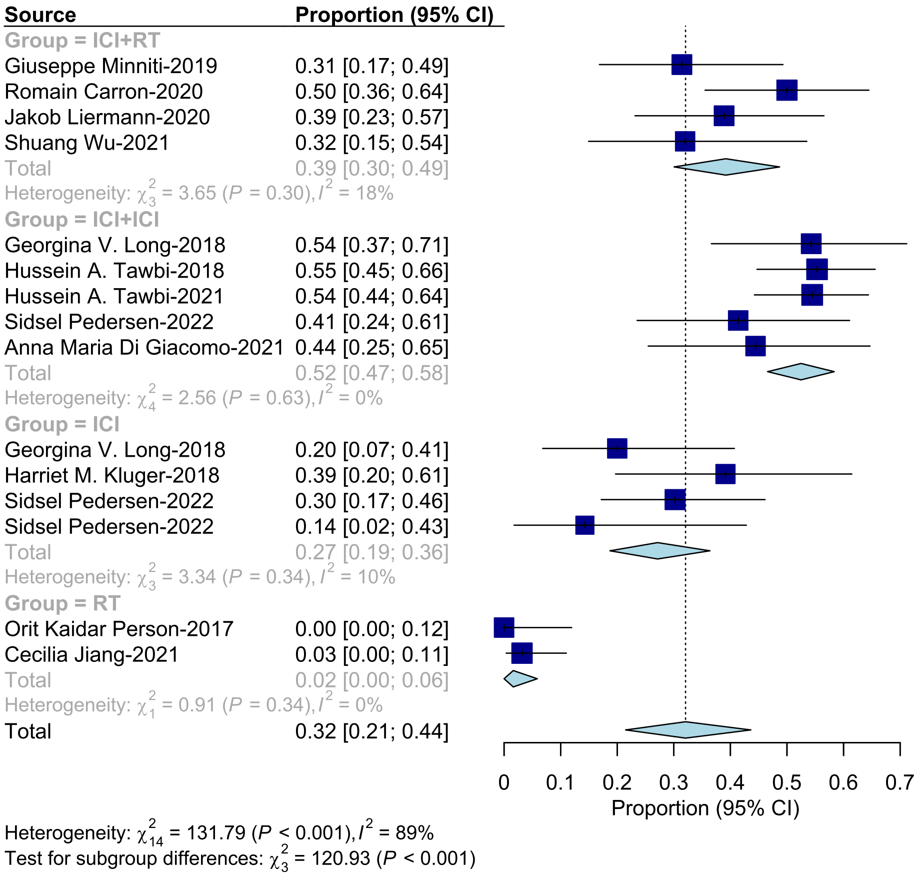


Fig. 6. Pooled analysis of the 2-year iPFS rate of patients with brain metastases from melanoma under four treatment modalities (ICI + RT, ICI + ICI, RT, and ICI). Note: RT. radiotherapy; ICI. Immune checkpoint inhibitor; *CI.* confidence interval; χ^2. Chi-square test, subscripts were degrees of freedom.

Table 4
Meta-regression summary of 1-year iPFS.

Subtype	RT		ICI		ICI + RT		ICI + ICI	
	OR (95% *CI*)	*P*-value	*OR* (95% *CI*)	*P*-value	*OR*(95% *CI*)	*P*-value	*OR*(95% *CI*)	*P*-value
RT	1	–	1.451	<0.0001	1.681	<0.0001	1.416	<0.0001
ICI	0.689	<0.0001	1	–	1.158	0.021	1.271	<0.0001
ICI + RT	0.595	<0.0001	0.863	0.021	1	–	1.097	0.066
ICI + ICI	0.542	<0.0001	0.787	<0.0001	0.911	0.066	1	–

Note: –, no data; RT, radiotherapy; ICI, immune checkpoint inhibitor; iPFS, intracranial progression-free survival.

Table 5
Meta-regression summary of 2-year iPFS.

Subtype	RT		ICI		ICI + RT		ICI + ICI	
	OR (95% *CI*)	*P*-value	*OR*(95% *CI*)	*P*-value	*OR* (95% *CI*)	*P*-value	*OR* (95% *CI*)	*P*-value
RT	1	–	1.483	<0.0001	1.681	<0.0001	1.907	<0.0001
ICI	0.674	<0.0001	1	–	1.133	0.049	1.285	<0.0001
ICI + RT	0.595	<0.0001	0.882	0.049	1	–	1.134	0.013
ICI + ICI	0.524	<0.0001	0.778	<0.0001	0.882	0.013	1	–

Note: –, no data; RT, radiotherapy; ICI, immune checkpoint inhibitor; iPFS, intracranial progression-free survival.

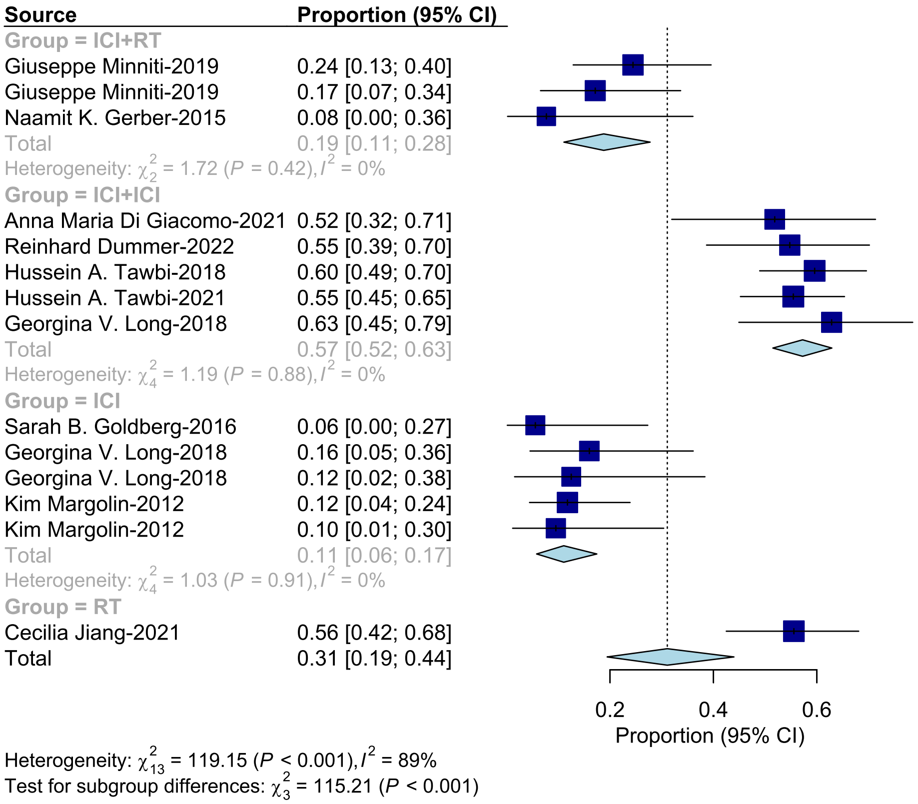


Fig. 7. Pooled analysis of the Grade 3 or 4 AE rate of patients with brain metastases from melanoma under four treatment modalities (ICI + RT, ICI + ICI, RT, and ICI). Note: RT. radiotherapy; ICI. Immune checkpoint inhibitor; *CI.* confidence interval; χ^2. Chi-square test, subscripts were degrees of freedom.

Table 6
Meta-regression summary of AEs over grade 3.

Subtype	RT		ICI		ICI + RT		ICI + ICI	
	OR (95% *CI*)	*P*-value	*OR* (95% *CI*)	*P*-value	*OR* (95% *CI*)	*P*-value	*OR* (95% *CI*)	*P*-value
RT	1	–	0.621	<0.0001	0.686	<0.0001	1.016	0.813
ICI	1.611	<0.0001	1	–	1.105	0.136	1.637	<0.0001
ICI + RT	1.457	<0.0001	0.905	0.136	1	–	1.481	<0.0001
ICI + ICI	0.984	0.813	0.611	<0.0001	0.675	<0.0001	1	–

Note: –, no data; RT, radiotherapy; ICI, immune checkpoint inhibitor; AE, adverse event.

optimization for poor long-term survival is needed in the future.

CRediT authorship contribution statement

Jialing Wen: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Xiangdi Meng:** Writing – original draft, Visualization, Software, Methodology, Formal analysis. **Wenchao Gu:** Software, Resources, Methodology. **Shenke Zhang:** Software, Resources, Methodology. **Li Sui:** Resources. **Gang Guo:** Resources. **Liang Yan:** Visualization, Resources. **Wangcai Ren:** Resources, Investigation, Data curation. **Xuanzhang Tu:** Visualization, Resources. **Kensuke Osada:** Writing – review & editing, Resources. **Takashi Shimokawa:** Writing – review & editing, Resources. **Yang Li:** Writing – review & editing, Supervision, Resources, Conceptualization. **Liqiu Ma:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

Funding

This work was supported by JSPS KAKENHI 26861029 and 17K16423, China National Nuclear Corporation Basic Research Foundation CNNC-JCYJ-202224, CIAE President's Strategic Grant YZ212404000801, and Grant-in-Aid for Young Scientifics from Gunma University 100215001E0205040400. L. Ma was supported by the IASCT 20th Research Encouragement Award for the Visiting Researcher from Overseas from International Association for the Sensitization of Cancer Treatment, China.

Declaration of competing interest

None.

Acknowledgments

The authors thank Dr. Qiaojuan Wang, Yue Wang, Ling Li and Shangmin Wen for their information collection.

Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radmp.2025.02.001.

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