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Immune Checkpoint Inhibitor with or without Radiotherapy in Melanoma Patients with Brain Metastases: A Systematic Review and Meta-Analysis

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Objective: Immune checkpoint inhibitor (ICI) therapy has shown activity against melanoma brain metastases. Recently, promising results have also been reported for ICI combination therapy and ICI combined with radiotherapy. We aimed to evaluate radiologic response and adverse event rates of these therapeutic options by a systematic review and meta-analysis.
Materials and Methods: A systematic literature search of Ovid-MEDLINE and EMBASE was performed up to October 12, 2019 and included studies evaluating the intracranial objective response rates (ORRs) and/or disease control rates (DCRs) of ICI with or without radiotherapy for treating melanoma brain metastases. We also evaluated safety-associated outcomes.
Results: Eleven studies with 14 cohorts (3 with ICI combination therapy; 5 with ICI combined with radiotherapy; 6 with ICI monotherapy) were included. ICI combination therapy {pooled ORR, 53% (95% confidence interval [CI], 44–61%); DCR, 57% (95% CI, 49–66%)} and ICI combined with radiotherapy (pooled ORR, 42% [95% CI, 31–54%]; DCR, 85% [95% CI, 63–95%]) showed higher local efficacy compared to ICI monotherapy (pooled ORR, 15% [95% CI, 11–20%]; DCR, 26% [95% CI, 21–32%]). The grade 3 or 4 adverse event rate was significantly higher with ICI combination therapy (60%; 95% CI, 52–67%) compared to ICI monotherapy (11%; 95% CI, 8–17%) and ICI combined with radiotherapy (4%; 95% CI, 1–19%). Grade 3 or 4 central nervous system (CNS)-related adverse event rates were not different (9% in ICI combination therapy; 8% in ICI combined with radiotherapy; 5% in ICI monotherapy).
Conclusion: ICI combination therapy or ICI combined with radiotherapy showed better local efficacy than ICI monotherapy for treating melanoma brain metastasis. The grade 3 or 4 adverse event rate was highest with ICI combination therapy, and the CNS-related grade 3 or 4 event rate was similar. Prospective trials will be necessary to compare the efficacy of ICI combination therapy and ICI combined with radiotherapy.
Keywords: *Immune checkpoint inhibitor; Immunotherapy; Radiation; Radiotherapy; Meta-analysis*

INTRODUCTION

Brain metastases from melanoma are common, with the reported incidence ranging from 10% to 75% in autopsy series (1-3). Historically, the prognosis of melanoma with brain metastases is dismal with the median survival being only 4 months (4, 5), and patients do not respond well to radiotherapy or cytotoxic chemotherapy alone (6, 7).

Recently, immune checkpoint inhibitor (ICI) therapy has attracted attention as it has shown a benefit in treating a

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variety of soft tissue malignancies including melanoma and non-small cell lung cancer (7, 8). Several clinical trials have reported ICI activity against advanced melanoma including melanoma brain metastases (9-14). ICI combination therapy (i.e., nivolumab and ipilimumab) showed promising results for treating melanoma brain metastases, with a reported intracranial objective response rate (ORR) of 46–55% (15-17). Additionally, stereotactic radiosurgery (SRS) is recommended as a local therapy for melanoma brain metastases in the National Comprehensive Cancer Network guidelines (9); several retrospective studies combining ICI and radiotherapy have also reported respectable efficacy (18-21).

There is a paucity of data from large-scale comparative studies to guide selection among the available therapeutic options. Rulli et al. (22) conducted a meta-analysis evaluating the efficacy of the several therapeutic options in melanoma brain metastases, but only two studies on ICI combined with radiotherapy were included. Furthermore, the safety issue was not covered. Thus, we aimed to investigate ICI monotherapy and combination therapy local efficacy and safety, with or without radiotherapy, for the treatment of melanoma brain metastases.

MATERIALS AND METHODS

This study was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (23).

Search Strategy and Eligibility Criteria

A literature search of the MEDLINE/PubMed and EMBASE databases was conducted using pertinent MeSH or EMTREE terms with common keywords for relevant articles until October 12, 2019. The search terms were as follows: ((melanoma)) AND ((brain metasta*) OR (intracranial)) AND ((CTLA4) OR (CTLA-4) OR (PD1) OR (PD-1) OR (PD-L1) OR (ipilimumab) OR (nivolumab) OR (pembrolizumab) OR (atezolizumab) OR (avelumab) OR (durvalumab)). The search was limited to the English language but not limited to human or animal or by publication date.

After eliminating duplicates, articles were screened based on the title and abstract. Full-text articles were then thoroughly assessed according to the following eligibility criteria: 1) population: malignant melanoma patients with brain metastasis; 2) intervention: ICI with or without radiotherapy; 3) comparator(s)/control: not applicable; 4) outcomes: intracranial objective response or disease control rate (DCR); and 5) study design: observational studies, clinical trials, and conference abstracts reporting the results of clinical trial but not published yet. We excluded studies that met any of the following criteria: 1) review; 2) case reports or case series including fewer than 10 patients; 3) conference abstracts; 4) letters, editorials, and comments; 5) animal studies; 6) studies with a partially overlapping patient cohort (for studies with an overlapping study population, the study with the largest population was selected); 7) phase I trial; and 8) studies with response assessment time not specified.

Data Extraction and Quality Assessment

A standardized extraction form was used to obtain the following information from the selected studies: 1) study characteristics: institution, study location, recruitment period, study design (retrospective vs. prospective vs. clinical trial); 2) demographic and clinical characteristics: number of treated patients/lesions, presence vs. absence of symptoms associated with melanoma brain metastasis; 3) characteristics associated with treatment: treatment arms (ICI monotherapy vs. ICI combined with radiotherapy vs. ICI combination therapy), ICI used (e.g., ipilimumab, pembrolizumab, and nivolumab), type(s) of RT if used (whole brain radiation therapy [WBRT] and/or SRS); and 4) characteristics associated with outcome: response assessment criteria, response assessment time after initiation of therapy. The quality of evidence in the included studies was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (24, 25). The GRADE system rates the quality of evidence from very low to high based on study design, risk of bias, imprecision, inconsistency, indirectness, magnitude of effect, dose-response relationship, and consideration of all plausible residual confounders.

Data Synthesis and Analysis

The primary study endpoints of this meta-analysis were 1) intracranial ORR (percentage of patients with melanoma brain metastases who were confirmed as achieving complete [CR] or partial response [PR]) and 2) intracranial DCR (percentage of patients with melanoma brain metastases who were confirmed as achieving CR, PR, or stable disease [SD]) assessed using response assessment criteria in the time each study prespecified. These were also pooled separately regarding the treatment arms (ICI monotherapy

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vs. ICI combined with radiotherapy vs. ICI combination therapy). Of note, intracranial ORR and DCR were pooled excluding symptomatic cohorts, as symptomatic cohorts are believed to show poor response rates (17, 26). In addition, intracranial CR rate was evaluated regarding the treatment arms.

We also evaluated safety-associated outcomes including treatment-related adverse events of any grade, grade 3 or 4 adverse events, central nervous system (CNS)-related events of any grade, and CNS-related grade 3 or 4 adverse events according to Common Terminology Criteria for Adverse Events v3.0 or v4.0, depending on each included study used. In addition, indirect comparisons were made between the treatment arms.

Meta-analytic pooling was based on the inverse variance method for calculating weights, and pooled estimates with their 95% confidence intervals (CI) were determined using DerSimonian–Laird random-effects modeling. Since grade 3 or 4 adverse events are rare, the pooled incidence rates of overall and CNS-related grade 3 or 4 adverse events were obtained with the binomial-normal model. In this, we calculated the pooled incidence using mixed-effects logistic regression models for dichotomous data, i.e., binomial-normal model, instead of an inverse-variance weighting model, which requires normality assumption (27, 28). Heterogeneity across studies was assessed using the Q test and I^2 statistic, with $I^2 > 50\%$ indicating the presence of heterogeneity (29-31). Publication bias was evaluated using the funnel plot and Egger's test (32, 33). In addition, to test if treatment arms as moderators have statistical effects in the meta-regression, we used a Wald-type chi-square test with multiplicity adjustment and the regression coefficient obtained to estimate the intervention effect and odds ratio (OR) from a reference group (34, 35). In addition, we performed sensitivity analysis in the ICI monotherapy group limited to ipilimumab to test whether type of ICI would be the source of heterogeneity and in the ICI combined with radiotherapy group limited to SRS to test whether mode of radiotherapy would be the source of heterogeneity. Statistical analyses were performed using R software (version 3.1.2; R Foundation for Statistical Computing) with the "meta" and the "metafor" packages. In the meta-regression analysis, we used the Knapp and Hartung adjustment, which typically used in the mixed effects meta-regression model, to control the Type 1 error rate of 0.05 for each analysis and reported multiplicity-adjusted *p* values and 95% CIs.

RESULTS

Literature Search

A flow chart of the publication selection process is summarized in Figure 1. Altogether, 392 non-duplicated studies were identified. Of these, 234 articles were excluded on the basis of their titles and abstract because of the following reasons: 1) conference abstract (n = 205) (except Tawbi et al. (17), reporting outcomes of nivolumab and ipilimumab combination therapy in patients with symptomatic melanoma brain metastases); 2) not in the field of interest (n = 48); 3) review (n = 13); 4) case report (n = 13); and 5) animal study (n = 2). Subsequently, 70 potentially eligible articles were assessed according to the eligibility criteria, and a further 59 studies were excluded because of the following reasons: 1) articles not reporting intracranial response rates (n = 32); 2) articles reporting intracranial and extracranial outcomes in an inseparable way (n = 10); 3) response assessment time not prespecified (n = 6); 4) studies with a partially overlapping patient cohort (n = 3); 4) articles including fewer than 10 patients (n = 2); 5) articles reporting outcomes in melanoma and non-melanoma patients in an inseparable way (n = 2); 6) articles reporting outcomes of ICI-only and ICI combined with radiotherapy in an inseparable way (n = 2); 7) summary of other study (n = 1); and 8) phase I trial (n = 1). Consequently, a total of 11 studies including 14 cohorts (divided depending on the treatment arms, what ICI used, and presence vs. absence of symptoms; 6 treated with ICI monotherapy; 5 treated with ICI combined with radiotherapy; 3 treated with ICI combination therapy) met the eligibility criteria and were included in the analysis (15-21, 26, 36-38).

Characteristics of the Included Studies

The detailed study characteristics are summarized in Table 1. Five of the 11 studies were phase II clinical trials (15-17, 26, 36), and the remainder were conducted using a retrospective design (18-21, 37, 38). Six studies were conducted as multicenter studies (15-17, 26, 37, 38). Modified versions of Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, immune-related Response Criteria (irRC), Response Assessment in Neuro-Oncology brain metastases (RANO-BM), modified WHO criteria, and RECIST v1.1 were used for tumor response assessment in four (15-17, 36), two (18, 20), two (21, 37), one (38), and one studies (19), respectively. Margolin et al. (26) used

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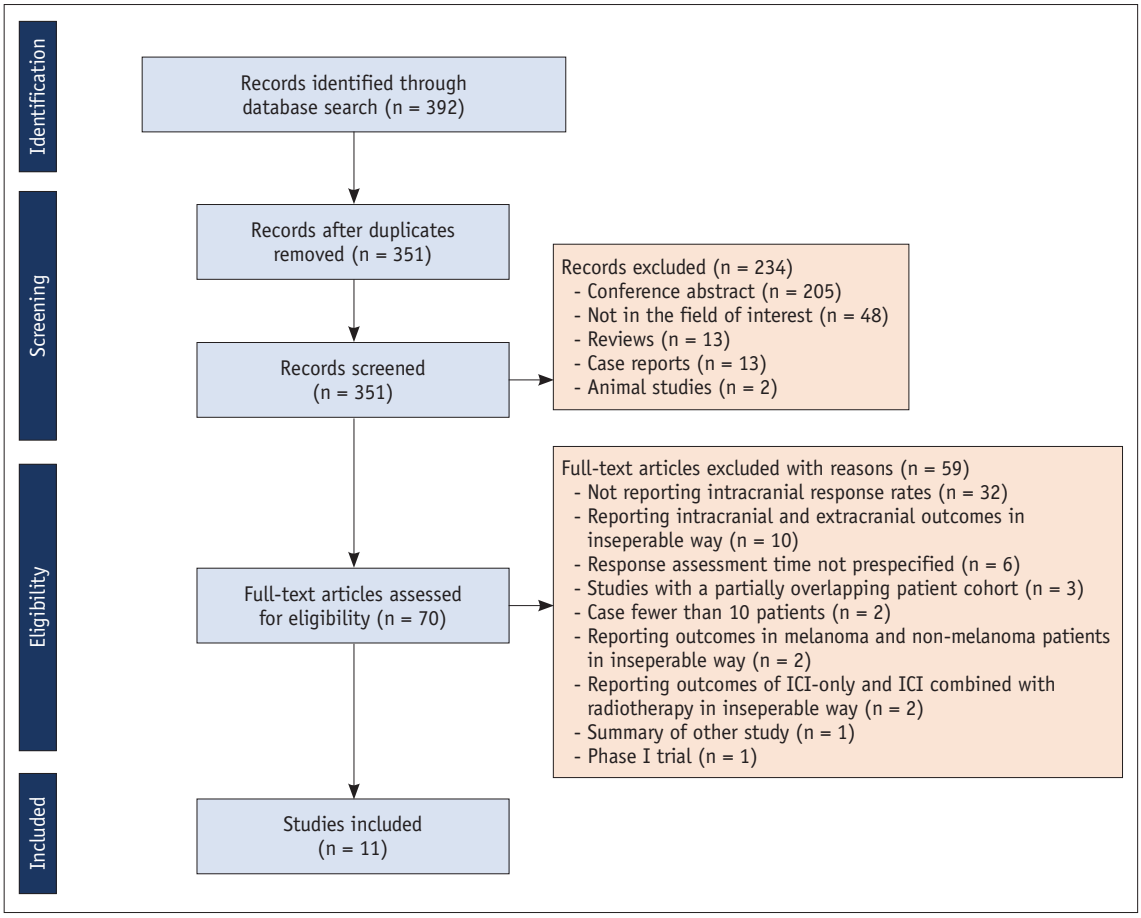

Fig. 1. Flow chart of the study selection process. ICI = immune checkpoint inhibitor

both modified WHO and irRC criteria, and we extracted the results based on modified WHO criteria for the meta-analytic pooling. Response assessment time after initiation of therapy varied across the studies, from 4 to 16 weeks. Three studies used nivolumab and ipilimumab combination therapy (15, 16). Three studies combined SRS with ICI monotherapy (18-20), and one study combined SRS or WBRT with monotherapy (21). Two studies focused on symptomatic melanoma brain metastasis (17, 26). Nine of the 11 studies (15, 16, 19, 21, 26, 36-38) conducted per-patient analysis, and the remaining two studies conducted per-lesion analysis (18, 20).

Quality Assessment

The five included clinical trials were initially rated with high certainty rate (15-17, 26, 36), and the six retrospective studies were initially rated with low certainty rate (18-21, 37, 38). In the risk of bias domain, two studies were down-rated as they performed per-lesion analysis (18, 20). In the imprecision domain, two studies were down-rated because of the widest 95% CI for the local efficacy among studies using the same treatment arms, derived from small sample size (21, 38). In addition, the study by Tawbi et al. (17) was down-rated because of the widest 95% CI for the grade 3 or 4 adverse events among the studies using ICI combination therapy. In the inconsistency domain, one study (21) was down-rated because of a large difference of local efficacy compared to other studies using ICI combined with radiotherapy. The study by Queirolo et al. (37) was up-rated due to a large effect size (comprising 145 out of 272 patients [53%] among the studies using ICI monotherapy study). Consequently, the quality of evidence was high in three (15, 16, 26), moderate in two (17, 37), low in one (19), and very low in four studies (18, 20, 21, 38).

Efficacy

The pooled intracranial ORR and DCR when excluding symptomatic cohorts are summarized in Table 2. Five (15, 26, 36-38), three (18, 20, 21), and two studies (15, 16) reported intracranial ORR when using ICI monotherapy, ICI

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Table 1. Characteristics of 14 Cohorts from 11 Included Studies

Authors (Publication Year)	Nation	Multicenter	Study Design	Recruitment Period	Response Criteria	Response Assessment Time after Initiation of Therapy (Weeks)	ICI Used	Radiotherapy	Symptoms	Analysis	Treated No.
ICI monotherapy											
Weber et al. (2011) (38)	USA	Yes	Retrospective	NR	mWHO	12	Ipilimumab	-	NR	Per-patient	12
Margolin et al. (2012) (26)	USA	Yes	Phase II trial	2008.7–2009.6	mWHO, irRC	12	Ipilimumab	-	Asymptomatic	Per-patient	51
Margolin et al. (2012) (26)	USA	Yes	Phase II trial	2008.7–2009.6	mWHO, irRC	12	Ipilimumab	-	Symptomatic	Per-patient	21
Queirolo et al. (2014) (37)	Italy	Yes	Retrospective	NR	irRC	12	Ipilimumab	-	Asymptomatic	Per-patient	145
Long et al. (2018) (15)	Australia	Yes	Phase II trial	2014.11–2017.4	mRECIST 1.1†	4	Nivolumab	-	Mixed	Per-patient	41
Kluger et al. (2019) (36)	USA	No	Phase II trial	2014.3–2015.8	mRECIST 1.1*	8	Pembrolizumab	-	Asymptomatic		
ICI combined with radiotherapy											
Silk et al. (2013) (21)	USA	No	Retrospective	2005–2012	irRC	4–16	Ipilimumab	WBRT/SRS	Mixed	Per-patient	22
Anderson et al. (2017) (18)	USA	No	Retrospective	2014.1–2015.12	RANO-BM	6–8	Pembrolizumab	SRS	NR	Per-lesion	23
Anderson et al. (2017) (18)	USA	No	Retrospective	2014.1–2015.12	RANO-BM	6–8	Ipilimumab	SRS	NR	Per-lesion	31
Nardin et al. (2018) (19)	France	No	Retrospective	2012–2015	RECIST 1.1	4	Pembrolizumab	SRS	Mixed	Per-patient	25
Trommer-Nestler et al. (2018) (20)	Germany	No	Retrospective	2011.8–2016.9	RANO-BM	12	Pembrolizumab/ nivolumab	SRS	NR	Per-lesion	28
ICI combination therapy											
Long et al. (2018) (15)	Australia	Yes	Phase II trial	2014.11–2017.4	mRECIST 1.1*	4	Nivolumab + ipilimumab	-	Asymptomatic	Per-patient	35
Tawbi et al. (2018) (16)	USA	Yes	Phase II trial	2015.2–2017.6	mRECIST 1.1‡	4	Nivolumab + ipilimumab	-	Asymptomatic	Per-patient	94
Tawbi et al. (2019) (17)	USA	Yes	Phase II trial	NR	mRECIST 1.1‡	4	Nivolumab + ipilimumab	-	Symptomatic	Per-patient	18

*Up to five target lesions of 5 mm or greater or at least twice the slice thickness if 2.5 mm or greater, †Up to five target lesions of 5–40 mm in diameter, ‡Up to five target lesions of 5–30 mm in diameter including target lesions measuring 5 to 10 mm in their longest diameter. ICI = immune checkpoint inhibitor, irRC = immune-related Response Criteria, mRECIST = modified RECIST, mWHO = modified World Health Organization, NR = not reported, RANO-BM = Response Assessment in Neuro-Oncology brain metastases, RECIST = Response Evaluation Criteria in Solid Tumors, SRS = stereotactic radiosurgery, WBRT = whole brain radiation therapy

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Table 2. Pooled Analysis of the Included Studies Evaluating Efficacy (Random-Effects Model)

Treatment Arm	Intracranial ORR			Intracranial DCR			Intracranial CR		
	Proportion	OR (95% CI)	*P*	Proportion	OR (95% CI)	*P*	Proportion	OR (95% CI)	*P*
ICI monotherapy	15 (11–20)	REF		26 (21–32)	REF		6 (2–14)	REF	
ICI combined with radiotherapy	42 (31–54)	1.32 (1.17–1.49)	< 0.01	85 (63–95)	1.94 (1.72–2.18)*	< 0.01	6 (1–37)	1.00 (0.99–1.01)	0.99
ICI combination therapy	53 (44–61)	1.48 (1.32–1.65)	< 0.01	57 (49–66)	1.37 (1.16–1.63)*	< 0.01	23 (17–32)	1.26 (1.05–1.50)	0.02
Total	29 (18–43)	-	-	54 (38–70)	-	-	10 (5–18)	-	-

Values are expressed as proportion (95% CI). OR was calculated based on indirect comparison. *Intracranial DCR was significantly higher when using ICI combined with radiotherapy compared to ICI combination therapy (OR [95% CI], 1.41 [1.20–1.67]; $p < 0.01$). CI = confidence interval, CR = complete response, DCR = disease control rate (proportion of the patients who were confirmed as CR, PR, or SD), OR = odds ratio, ORR = objective response rate (proportion of the patients who were confirmed as CR or PR), PR = partial response, REF = reference category, SD = stable disease

combined with radiotherapy, and ICI combination therapy, respectively.

Efficacy: ORR

Pooled intracranial ORR based on random-effects modeling was 15% (11–20%; $I^2 = 0\%$), 42% (31–54%; $I^2 = 26\%$), and 53% (95% CI, 44–61%; $I^2 = 0\%$) when using ICI monotherapy, ICI combined with radiotherapy, and ICI combination therapy, respectively. There was no substantial heterogeneity observed in all three treatment arms. The overall intracranial ORR was 29% (95% CI, 18–43%), with a substantial heterogeneity ($I^2 = 87\%$; $p < 0.01$) (Fig. 2). There was no significant publication bias observed in the Deeks funnel plot ($p = 0.24$). Compared to ICI monotherapy, intracranial ORR was significantly higher when using ICI combined with radiotherapy (OR [95% CI], 1.32 [1.17–1.49]; $p < 0.01$) and ICI combination therapy (OR [95% CI], 1.48 [1.32–1.65]; $p < 0.01$). There was no significant difference of intracranial ORR between ICI combined with radiotherapy and ICI combination therapy.

Efficacy: DCR

Five (15, 26, 36-38), four (18-21), and two studies (15, 16) reported intracranial DCR when using ICI monotherapy, ICI combined with radiotherapy, and ICI combination therapy, respectively. Pooled intracranial DCR based on random-effects modeling was 26% (21–32%; $I^2 = 0\%$), 85% (63–95%; $I^2 = 79\%$), and 57% (95% CI, 49–66%; $I^2 = 0\%$) when using ICI monotherapy, ICI combined with radiotherapy, and ICI combination therapy, respectively. There was a substantial heterogeneity observed in ICI combined with radiotherapy ($p < 0.01$). The overall intracranial DCR was 54% (95% CI, 38–70%), with a substantial heterogeneity ($I^2 = 90\%$; $p < 0.01$) (Fig. 2). There was no significant publication bias observed in the Deeks funnel plot ($p = 0.14$). Compared to ICI monotherapy, intracranial DCR was significantly higher when using ICI combined with radiotherapy (OR [95% CI], 1.94 [1.72–2.18]; $p < 0.01$) and ICI combination therapy (OR [95% CI], 1.37 [1.16–1.63]; $p < 0.01$). In addition, intracranial DCR was significantly higher when using ICI combined with radiotherapy compared to ICI combination therapy (OR [95% CI], 1.41 [1.20–1.67]; $p < 0.01$).

Efficacy: CR

Five (15, 26, 36-38), three (18, 20, 21), and two studies (15, 16) reported intracranial CR rates when using ICI monotherapy, ICI combined with radiotherapy, and ICI combination therapy, respectively. Pooled intracranial CR rate based on random-effects modeling was 6% (2–14%; $I^2 = 57\%$), 6% (1–37%; $I^2 = 69\%$), and 23% (95% CI, 17–32%; $I^2 = 0\%$) when using ICI monotherapy, ICI combined with radiotherapy, and ICI combination therapy, respectively. There was a substantial heterogeneity observed in ICI monotherapy ($p = 0.06$) and ICI combined with radiotherapy ($p = 0.04$). The overall pooled intracranial CR rate was 10% (95% CI, 5–18%), with a substantial heterogeneity ($I^2 = 74\%$; $p < 0.01$) (Supplementary Fig. 1). There was a significant publication bias observed in the Deeks funnel plot ($p < 0.01$). The intracranial CR rate of ICI combination therapy was significantly higher compared to ICI monotherapy (OR [95% CI], 1.26 [1.05–1.50]; $p = 0.02$) but not different compared to ICI combined with radiotherapy (OR [95% CI], 1.00 [0.99–1.01]; $p = 0.99$).

Efficacy in Symptomatic Cohort

Margolin et al. (26) reported the efficacy of ICI monotherapy (ipilimumab) for the symptomatic cohorts,

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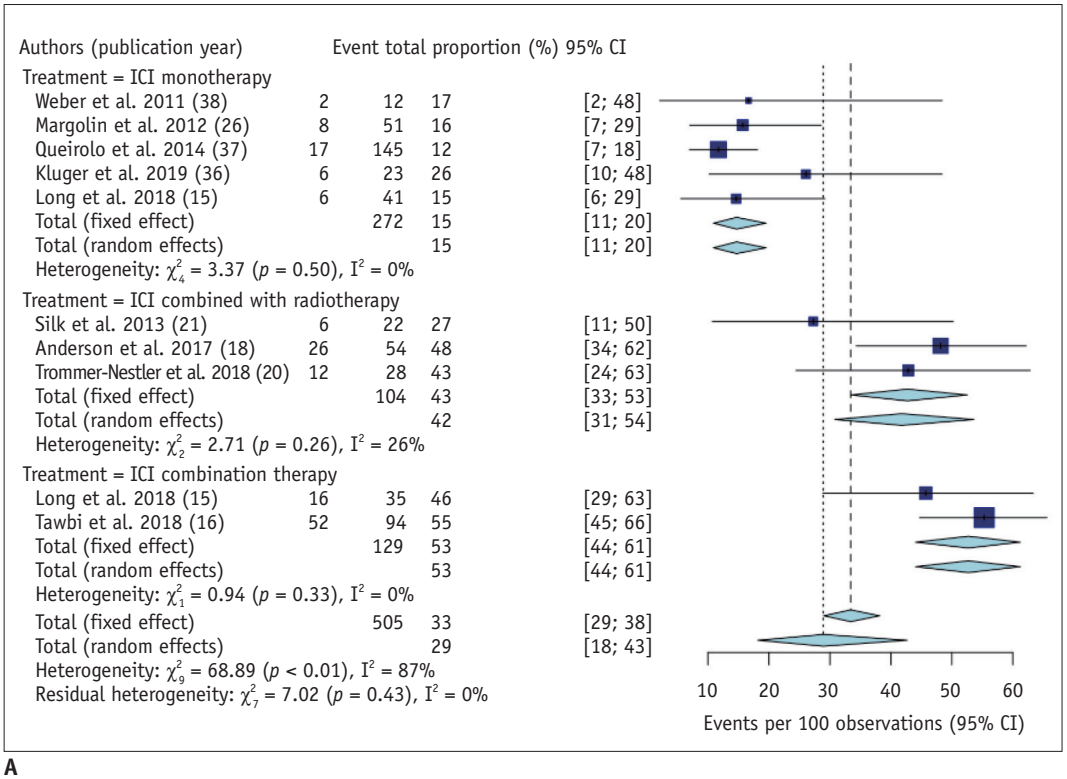

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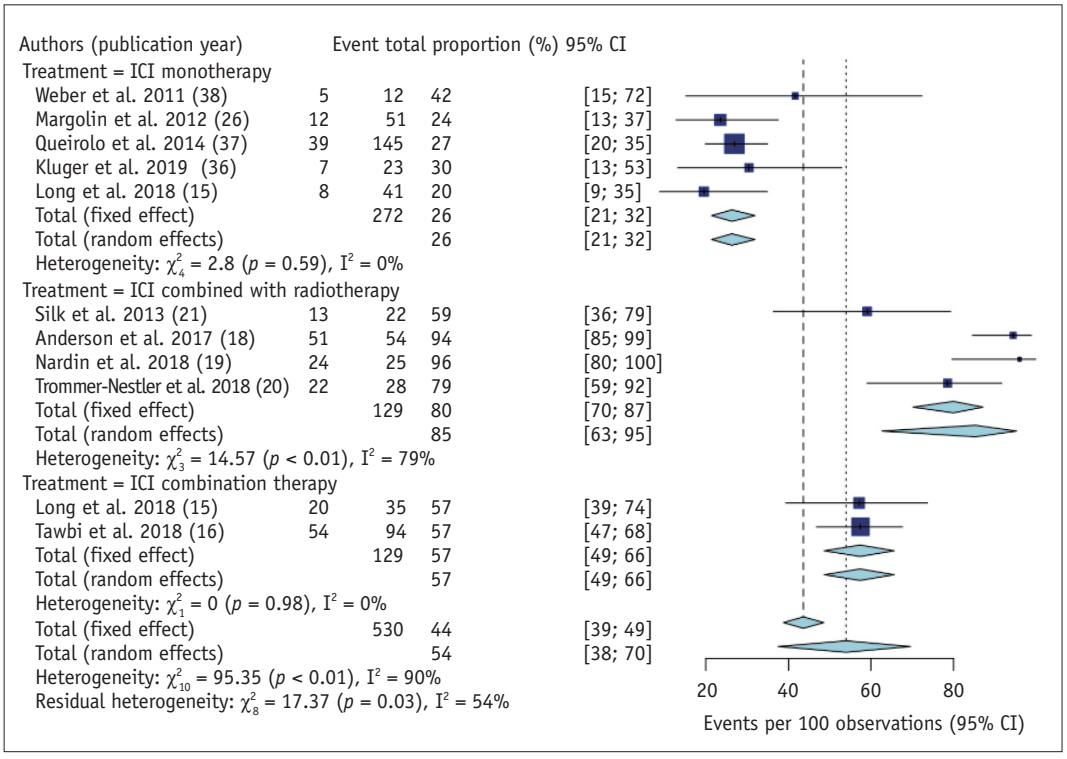

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Fig. 2. Forest plot of the intracranial (A) objective response rates and (B) disease control rates excluding symptomatic cohorts.
Intracranial objective response rate was significantly higher when using ICI combined with radiotherapy (42%; 95% CI, 31–54%) and ICI combination therapy (53%; 95% CI, 44–61%) compared to ICI monotherapy (15%; 95% CI, 11–20%). Intracranial disease control rate was also significantly higher when using ICI combined with radiotherapy (85%; 95% CI, 63–95%) and ICI combination therapy (57%; 95% CI, 49–66%) compared to ICI monotherapy (26%; 95% CI, 21–32%). CI = confidence interval

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with the ORR, DCR, and CR rate of 5% (1/21), 10% (2/21), and 5% (1/21), respectively. Tawbi et al. (17) reported the efficacy of ICI combination therapy for the symptomatic cohorts, with the ORR, DCR, and CR rate of 17% (3/18), 22% (4/18), and 11% (2/18), respectively.

Safety

The pooled grade 3 or 4 adverse event rates regarding the treatment arms are summarized in Table 3, and the details of adverse events are summarized in Supplementary Table 1. In addition, information on any grade adverse event rates and CNS-related adverse event rates is described in Supplementary Materials and presented as the forest plots in Supplementary Figure 2.

Safety: Grade 3 or 4 Adverse Event

Two (15, 37), two (18, 20), and three studies (15-17) reported grade 3 or 4 adverse event rates when using ICI monotherapy, ICI combined with radiotherapy, and ICI combination therapy, respectively. The pooled grade 3 or 4 adverse event rates were 11% (8–17%; I^2 = 0%), 4% (1–19%; I^2 = 0%), and 60% (95% CI, 52–67%; I^2 = 0%) when using ICI monotherapy, ICI combined with radiotherapy, and ICI combination therapy, respectively. The overall grade 3 or 4 adverse event rate was 26% (95% CI, 10–52%) with a substantial heterogeneity (I^2 = 93%; p < 0.01) (Supplementary Fig. 3). There was no significant publication bias observed in the Deeks funnel plot (p = 0.40). The grade 3 or 4 adverse event rate was significantly higher when using ICI combination therapy compared to ICI monotherapy (OR [95% CI], 11.72 [5.29–25.95]; p < 0.01) and ICI combined with radiotherapy (OR [95% CI], 49.22 [2.83–856.62]; p = 0.02).

Safety: Grade 3 or 4 CNS-Related Adverse Event

Five (15, 26, 36-38), three (18-20), and three studies (15-17) reported grade 3 or 4 CNS-related adverse event rates when using ICI monotherapy, ICI combined with radiotherapy, and ICI combination therapy, respectively. The pooled grade 3 or 4 CNS-related adverse event rates were 5% (3–8%; I^2 = 8%), 8% (3–20%; I^2 = 0%), and 9% (95% CI, 5–15%; I^2 = 0%) when using ICI monotherapy, ICI combined with radiotherapy, and ICI combination therapy, respectively. The overall grade 3 or 4 CNS-related adverse event rate was 7% (95% CI, 5–9%), without heterogeneity (I^2 = 3%; p = 0.41) (Supplementary Fig. 3). There was no significant publication bias observed in the Deeks funnel plot (p = 0.88). Grade 3 or 4 CNS-related adverse event rates were not significantly different between the three arms.

Sensitivity Analysis

To test whether types of ICI (anti-cytotoxic T-lymphocyte antigen 4 [anti-CTLA-4; ipilimumab] vs. anti-programmed death 1 [anti-PD 1; nivolumab and pembrolizumab]) were the source of heterogeneity, we performed sensitivity analysis in the ICI monotherapy group. Three cohorts used anti-CTLA-4 drugs (26, 37, 38), and the other two cohorts used anti-PD-1 drugs (15, 36). The pooled estimates were robust against types of ICI except intracranial CR; compared to anti-CTLA-4, anti-PD-1 drugs showed higher intracranial CR (12% [95% CI, 5–26%; I^2 = 0%] vs. 3% [95% CI, 1–6%; I^2 = 31%]; p < 0.01) (Supplementary Table 2).

To test whether mode of radiotherapy was the source of heterogeneity, we performed sensitivity analysis in the ICI combined with radiotherapy group. In a study by Silk et al. (21), WBRT and SRS was used in 48.5% and 51.5% of the patients, respectively. The other three cohorts only used SRS (18-20). Since Silk et al. (21) did not report the data regarding adverse events, sensitivity analysis was possible only in response rates. Intracranial ORR (42% [95% CI, 31–54%] to 46% [95% CI, 36–57%]; p = 0.11), DCR (85% [95% CI, 63–95%] to 91% [95% CI, 74–97%]; p = 0.10), and CR (6% [95% CI, 1–37%] to 9% [95% CI, 1–59%];

Table 3. Pooled Analysis of the Included Studies Evaluating Safety (Random-Effects Model)

Treatment Arm	Grade 3/4 AE			CNS-Related Grade 3/4 AE		
	Proportion	OR (95% CI)	*P*	Proportion	OR (95% CI)	*P*
ICI monotherapy	11 (8–17)	REF		5 (3–8)	REF	
ICI combined with radiotherapy	4 (1–19)	0.24 (0.01–4.29)*	0.24	8 (3–20)	1.70 (0.43–6.73)	0.40
ICI combination therapy	60 (52–67)	11.72 (5.29–25.95)*	< 0.01	9 (5–15)	2.08 (0.79–5.50)	0.12
Total	26 (10–52)	-	-	7 (5–9)	-	-

Values are expressed as proportion (95% CI). OR was calculated based on indirect comparison. *Grade 3/4 AE rate was significantly higher when using ICI combination therapy compared to ICI combined with radiotherapy (OR [95% CI], 49.22 [2.83–856.62]; p = 0.02). AE = adverse event, CNS = central nervous system

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p = 0.56) slightly increased when excluding the Silk et al. (21) study but did not show statistically significant difference (Supplementary Table 3).

DISCUSSION

This meta-analysis showed that intracranial ORR and DCR were significantly higher when using ICI combined with radiotherapy (pooled ORR, 42%; DCR, 85%) or ICI combination therapy (pooled ORR, 53%; DCR, 57%) compared to ICI monotherapy (pooled ORR, 15%; DCR, 26%). Intracranial DCR was highest when using ICI combined radiotherapy, and intracranial CR rate was highest when using ICI combination therapy (23%). In terms of safety, the grade 3 or 4 adverse event rate was significantly higher with ICI combination therapy (60%) compared to ICI monotherapy (11%) and ICI combined with radiotherapy (4%), but grade 3 or 4 CNS-related adverse event rates were not significantly different across the treatment arms (5% in ICI monotherapy, 8% in ICI combined with radiotherapy, 9% in ICI combination therapy). Except for differences in intracranial CR depending on types of ICI used, response rates were not statistically different depending on types of ICI or mode of radiotherapy.

In several studies, ipilimumab (anti-CTLA 4) combined with nivolumab (anti-PD 1) has shown superior efficacy compared to ipilimumab alone for metastatic melanoma (39, 40). Similarly, for melanoma brain metastases, a study by Long et al. (15) showed better intracranial response when using nivolumab combined with ipilimumab compared to nivolumab alone. The largest single-arm trial, conducted by Tawbi et al. (16), showed intracranial ORR and DCR of nivolumab and ipilimumab combination therapy to be 55% and 57%, respectively. Our study reaffirmed the superior local efficacy of ICI combination therapy compared to ICI monotherapy. Meanwhile, the pooled grade 3 or 4 adverse event was also significantly higher with ICI combination therapy. Most but not all reported grade 3 or 4 adverse events resolved after appropriate management following safety guideline. The pooled CNS-related grade 3 or 4 events with ICI combination therapy were similar to other treatment arms.

Radiotherapy has been used to potentially enhance efficacy of ICI monotherapy for melanoma brain metastases, and our study demonstrated better local efficacy of ICI combined with radiotherapy. In addition, ICI combined with radiotherapy showed better intracranial DCR compared to ICI combination therapy, which indicates a higher proportion of tumors maintain a stable state when using ICI combined with radiotherapy. The synergistic effect of combining radiotherapy may be explained by the fact that radiation increases permeability of the blood-brain barrier (41), induces mitotic cell death, and releases tumor cell antigens, which can stimulate a cytotoxic immune response (42), and activates immune cells to attack tumor cells outside of irradiated zone, i.e., the abscopal effect (43). Furthermore, our study showed that the pooled grade 3 or 4 adverse events when using ICI combined with radiotherapy were not significantly different compared with ICI monotherapy. One of the specific concerns of using of radiotherapy is radionecrosis. Although still controversial, increased incidence of radionecrosis when using SRS combined with ICI compared to SRS alone cannot be excluded, considering previous results (44-47). The reported incidence of radionecrosis in treating melanoma brain metastases has been 0–38% (18, 19, 44-48) with the meta-analytic pooled incidence of 5.3% (49). Further studies are required to clarify this issue.

The included studies used various response assessment criteria. In 2015, the RANO working group announced RANO-BM criteria, which has recently gained wide acceptance. In contrast to WHO or RECIST criteria, mainly used for solid tumors of the body, RANO-BM was developed solely for evaluating treatment response of brain metastasis. Of note, only RANO-BM criteria consider pseudoprogression when evaluating the therapeutic response of ICI and SRS. Pseudoprogression can be considered when an image mimics local progression after initiation of the treatment but decreases rapidly on subsequent imaging. Regarding extracranial melanoma, the reported incidence of pseudoprogression ranged from 5% to 10% (50-52). In our included studies, incidence of pseudoprogression was 4% after pembrolizumab monotherapy (36) and 8–14% after ICI combined radiotherapy (19, 20).

There are several limitations of note. First, this meta-analysis was conducted using study-level data without detailed patient-level data. Second, all included studies on ICI combined with radiotherapy were conducted using a retrospective design, decreasing the comparability with the other treatment arms. Furthermore, because not all studies on ICI combined with radiotherapy reported both CNS-related grade 3 or 4 and grade 3 or 4 adverse event rates, comparison of these two pooled adverse event rates was limited. For example, only the grade 3 or 4 adverse

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event rate (not CNS-related grade 3 or 4 adverse event rate) was available in the study by Nardin et al. (19), which created a discrepancy between two pooled rates. Therefore, large prospective trials investigating the outcomes of ICI combined with radiotherapy, especially focusing on the comparison with ICI combination therapy, seem to be necessary. Third, thorough meta-regression analysis considering clinically important factors, i.e., metastatic burden, associated symptoms, and response criteria, to adjust response criteria effect was not feasible due to insufficient data. Regardless, this study-level meta-analysis provides important information for future practice and research.

In conclusion, ICI combination therapy and ICI combined with radiotherapy showed better local efficacy than ICI monotherapy for treating melanoma brain metastases. Overall, grade 3 or 4 adverse events were more frequent when using ICI combination therapy while CNS-related grade 3 or 4 adverse events were not statistically different across the three arms. However, since our analyses were based on indirect comparison and thorough meta-regression analysis was not available, prospective trials will be necessary to compare the efficacy of ICI combination therapy and ICI combined with radiotherapy.

Supplementary Materials

The Data Supplement is available with this article at https://doi.org/10.3348/kjr.2020.0728.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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