



# Immune checkpoint inhibitor therapy may increase the incidence of treatment-related necrosis after stereotactic radiosurgery for brain metastases: a systematic review and meta-analysis

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## Abstract

**Objectives** To compare the incidence of treatment-related necrosis between combination SRS+ICI therapy and SRS therapy alone in patients with brain metastases from melanoma and non-small cell lung cancer (NSCLC).

**Methods** A systematic literature search of Ovid-MEDLINE and EMBASE was performed up to August 10, 2020. The difference in the pooled incidence of treatment-related necrosis after SRS+ICI or SRS alone was evaluated. The cumulative incidence of treatment-related necrosis at the specific time point after the treatment was calculated and plotted. Subgroup and meta-regression analyses were additionally performed.

**Results** Sixteen studies (14 on melanoma, 2 on NSCLC) were included. In NSCLC brain metastasis, the reported incidences of treatment-related necrosis in SRS+ICI and SRS alone ranged 2.9–3.4% and 0–2.9%, respectively. Meta-analysis was conducted including 14 studies on melanoma brain metastasis. The incidence of treatment-related necrosis was higher in SRS+ICI than SRS alone (16.0% vs. 6.5%;  $p = 0.065$ ; OR, 2.35). The incidence showed rapid increase until 12 months after the SRS when combined with ICI therapy (14%; 95% CI, 8–22%) and its pace of increase slowed thereafter. Histopathologic diagnosis as the reference standard for treatment-related necrosis and inclusion of only symptomatic cases were the source of heterogeneity in SRS+ICI.

**Conclusions** Treatment-related necrosis tended to occur 2.4 times more frequently in the setting of combination SRS+ICI therapy compared with SRS alone in melanoma brain metastasis showing high cumulative incidence within the first year. Treatment-related necrosis should be considered when SRS+ICI combination therapy is used for melanoma brain metastasis, especially in the first year.

## Key Points

- Treatment-related necrosis occurred 2.4 times more frequently in the setting of combination SRS+ICI therapy compared with SRS alone in melanoma brain metastasis.
- Treatment-related necrosis more frequently occurred in brain metastases from melanoma than NSCLC.
- Reference standard for treatment-related necrosis and inclusion of only symptomatic treatment-related necrosis were a significant source of heterogeneity, indicating varying definitions of treatment-related necrosis in the literature need to be unified.

**Keywords** Immunotherapy · Radiation · Radiosurgery · Neoplasm metastasis · Necrosis

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## Abbreviations and acronyms

CI	Confidence interval
ICI	Immune checkpoint inhibitor
KM curve	Kaplan–Meier curve
NSCLC	Non-small cell lung cancer
SRS	Stereotactic radiosurgery

## Introduction

Brain metastases develop in approximately 40% of adult cancer patients [1, 2]. The most common primary malignancies that result in brain metastases are lung cancer and melanoma [3]. Non-small cell lung cancer (NSCLC) has the higher prevalence of the two malignancies. At diagnosis, 16–27% of patients with NSCLC have brain metastases while the 5-year cumulative incidence of brain metastasis in patients with NSCLC has been reported at 20–25% [4, 5]. Melanoma has a high tendency to metastasize to the brain: 28% of patients with metastatic melanoma have brain metastases at the time of diagnosis [5] while the reported incidence in autopsy cases has been up to 75% [6–8]. In the USA, approximately 50,000 patients with NSCLC or melanoma develop brain metastases every year [9].

Radiation therapy is one of the most commonly used therapies for brain metastases, as recommended in National Comprehensive Cancer Network (NCCN) guidelines, in part because few systemic agents penetrate the blood-brain barrier [10]. The most significant toxicity of brain-directed stereotactic radiosurgery (SRS) is treatment-related necrosis. Approximately 30% of treated lesions increase in size and change their pattern of contrast enhancement as a response to SRS, with a peak at 12–18 months after radiation therapy [11]. Recently, several studies demonstrated the synergistic effect of systemic immune check point inhibitor (ICI) therapeutics in patients treated with SRS [12–14]. However, published literature have also suggested an association between the use of ICI and development of treatment-related necrosis [15, 16].

We performed a systematic review and meta-analysis to evaluate and compare the incidence of treatment-related necrosis between combination SRS+ICI therapy and SRS therapy alone in patients with brain metastases from NSCLC and melanoma.

## Materials and methods

This study was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [17].

## 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 August 10, 2020. The search terms were as follows: ((brain metastas\*) AND ((treatment-related necrosis) OR (radionecrosis)) AND ((immunotherapy) OR (immune checkpoint inhibitor) OR (immune checkpoint blockade) OR (CTLA4) OR (CTLA-4) OR (PD1) OR (PD-1) OR (PD-L1) OR (ipilimumab) OR (nivolumab) OR (pembrolizumab))). The search was not limited by language, human, animal study, or publication date.

After eliminating duplicates, articles were screened on the basis of the title and abstract. Full-text articles were assessed according to the following eligibility criteria: (a) population: patients with brain metastasis from melanoma or NSCLC; (b) intervention: SRS with ICI; (c) comparator(s)/control: SRS alone; (d) outcomes: incidence of treatment-related necrosis; (e) study design: not limited. We excluded studies that met any of the following criteria: (a) review; (b) case reports or case series including fewer than 10 patients; (c) conference abstracts; (d) letters, editorials, reply, and comments; (e) animal studies; (f) studies on pediatric patients; (g) studies with a partially overlapping patient cohort (for studies with an overlapping study population, the study with the largest population was selected). The literature search and criteria application were conducted independently by two authors (P.H.K. and C.H.S., with 3 and 7 years of experience in performing systematic reviews and meta-analyses, respectively). Any discrepancies were resolved via consensus meeting.

## Data extraction and quality assessment

A standardized extraction form was used to obtain the following information from the selected studies: (a) study characteristics: institution and nation, recruitment period, study design (retrospective vs. prospective); (b) demographic and clinical characteristics: primary malignancy (melanoma vs. NSCLC), number of treated patients/lesions, age and sex distribution of the study population, follow-up period; (c) characteristics associated with the diagnosis of treatment-related necrosis: reference standard (clinical and radiologic diagnosis vs. histopathologic diagnosis), clinicoradiologic definition of treatment-related necrosis, presence vs. absence of associated symptoms; (d) characteristics associated with treatment: treatment used (SRS+ICI vs. SRS), ICI used (e.g., ipilimumab, pembrolizumab, and nivolumab), dose of ICI, timing of ICI (e.g., before SRS, after SRS, or concurrent use), mode of RT, dose, fraction, and gross target volume; (e) characteristics associated with outcome: incidence of treatment-related necrosis, interval from the treatment to the diagnosis of treatment-related necrosis if available. The quality of evidence in the

included studies was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [18, 19]. 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. The data extraction and quality assessment were conducted independently by two authors (P.H.K. and C.H.S., with 3 and 7 years of experience in performing systematic reviews and meta-analyses, respectively). Any discrepancies were resolved via consensus meeting.

## Data synthesis and analysis

The primary study outcome of this meta-analysis was the difference in the incidence of treatment-related necrosis after the use of combination SRS+ICI therapy vs. SRS therapy alone. The incidences of treatment-related necrosis reported in each included study were pooled separately based upon the treatment groups. Meta-analytic pooling was based on the inverse variance method for calculating weights so as to give more importance to larger studies, and the pooled estimates with their 95% confidence intervals (CI) were determined using DerSimonian–Laird random-effects modeling. In addition, between-study heterogeneity was assessed using the Q test and  $I^2$  statistic, with  $I^2 > 50\%$ , indicating the presence of heterogeneity [20–22]. Publication bias was evaluated using the funnel plot and Egger’s test [23, 24]. Publication bias-adjusted estimates were also obtained using the trim and fill method if significant publication bias was noted. Indirect comparisons were then made between the treatment groups, and odds ratio (OR) with 95% CI was additionally calculated. Direct comparison, which only included studies providing direction comparison between SRS+ICI and SRS groups, was also performed, also expressed as ORs with 95% CI.

In addition, the cumulative incidence of treatment-related necrosis at the specific time point after the treatment (including 95% CIs) was calculated and plotted. For this, Engauge Digitizer (Version 10.7; <http://markummittchell.github.io/engauge-digitizer>) was used to extract cumulative incidence of treatment-related necrosis at the specific time point based on the Kaplan–Meier (KM) curves provided in the study if available. Then, the cumulative incidence at each specific time point was meta-analytically pooled using the restricted maximum-likelihood estimation of random-effects model.

Subgroup and meta-regression analyses were additionally performed to identify the source of heterogeneity and to demonstrate the incidence of treatment-related necrosis in each subgroup. In the analysis, the study in which both clinical and radiologic and histopathologic diagnoses were used as the reference standard was categorized into clinical and radiologic diagnosis subgroups.

Statistical analyses were performed using R software (version 3.1.2; R Foundation for Statistical Computing) with the “meta” and the “metafor” packages, and line graphs were drawn with the “ggplot2” package. In the indirect comparison and meta-regression analysis,  $p < 0.05$  was considered statistically significant.

## Results

### Literature search

A flowchart of the publication selection process is summarized in Fig. 1. A total of 159 non-duplicated studies were identified. Of these, 124 articles were excluded on the basis of their titles and abstract because of the following reasons: (a) conference abstract ( $n = 83$ ); (b) not in the field of interest ( $n = 67$ ); (c) reviews ( $n = 41$ ); (d) case reports ( $n = 5$ ); (e) editorials ( $n = 5$ ); (f) animal studies ( $n = 3$ ); (g) reply ( $n = 2$ ); and (h) studies on pediatric population ( $n = 1$ ). Subsequently, 35 potentially eligible articles were assessed according to the eligibility criteria, and 19 additional studies were excluded because of the following reasons: (a) articles reporting incidence of treatment-related necrosis but including target primary tumor (i.e., melanoma and NSCLC) and non-target tumor in an inseparable way ( $n = 8$ ); (b) articles not reporting the incidence of treatment-related necrosis ( $n = 6$ ); (c) studies with a partially overlapping patient cohort ( $n = 4$ ); and (d) articles reporting the incidence of treatment-related necrosis but including SRS+ICI and SRS-alone groups in an inseparable way ( $n = 1$ ). Consequently, a total of 16 studies including 16 cohorts using SRS+ICI [12–14, 16, 25–36] and 8 cohorts using SRS [12, 14, 16, 25, 26, 29, 31, 35] met the eligibility criteria and were included in the analysis.

### Characteristics of the included studies

The detailed study and patient characteristics are summarized in Table 1. All included studies were conducted as a retrospective design, and two studies were conducted as multicenter studies [13, 28]. All but three studies were conducted in the USA [12–14, 16, 25–27, 29, 31, 33–36]. Primary tumors of the brain metastases were melanoma in 14 studies [13, 14, 16, 25–34, 36], and NSCLC in the other two studies [12, 35]. Fourteen of 16 studies conducted the per-patient analysis [12, 13, 16, 25–30, 32–36], and the other two studies conducted the per-lesion analysis [14, 31].

The detailed characteristics associated with the diagnosis of treatment-related necrosis are summarized in Table 2. Reference standards for the diagnosis of treatment-related necrosis were variable and variably reported. The histopathologic diagnosis was used as the reference standard in four studies [14, 33–35], and the

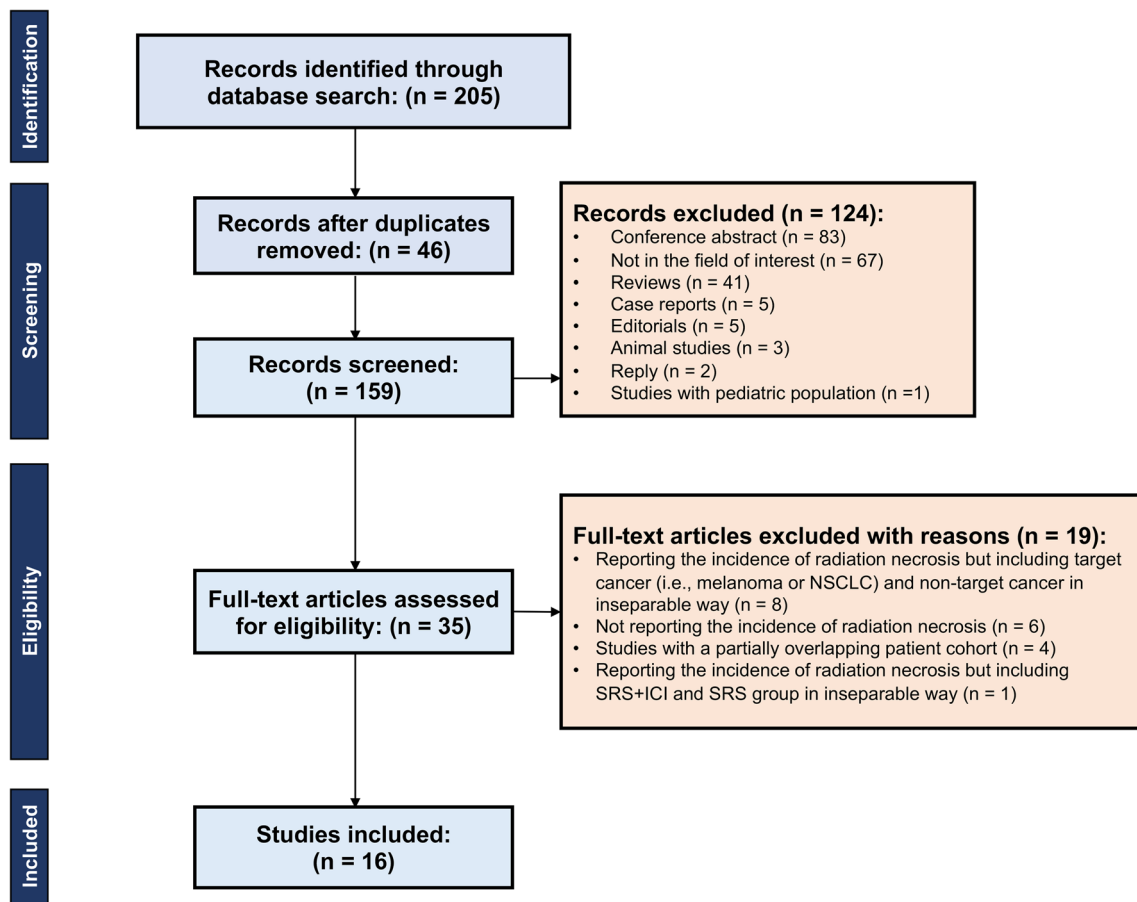


Fig. 1 Flowchart of the study selection process

clinical and radiologic diagnosis was used as the reference standard in seven studies [12, 13, 16, 27, 29, 30, 32]. In four studies, both histopathologic diagnosis and the clinical and radiologic diagnosis was used as the reference standard [16, 28, 31, 36]. The clinical and radiologic definition of treatment-related necrosis is highly variable across the studies. Ten studies defined clinicoradiologic treatment-related necrosis [12, 13, 16, 27–32, 36], and the most common element for the diagnosis of treatment-related necrosis was stable or improved radiographic findings during the follow-up, which was used in seven studies [13, 16, 27, 28, 30, 31, 36] (Table 2). However, only two studies elucidated the exact follow-up period for the diagnosis (“6 months” in Minniti et al [13] and “two consecutive scans” in Pires da Silva I et al [28]). Furthermore, only two studies specified in the definition that the location of the treatment-related necrosis was the same location previously irradiated [13, 29]. No studies specified the minimum interval between the radiation and necrosis for the diagnosis. Two studies mentioned conventional MR features indicating necrosis in their definitions (e.g., enhancing lesion with a central area of necrosis, peripheral enhancement, and central hypointensity) [28, 30]. Six studies [27–32] used

advanced MRI techniques for the diagnosis, including perfusion imaging [27, 29–32] and MR spectroscopy [29, 32]. Two studies used FDG-PET for the diagnosis of the treatment-related necrosis [28, 31]. The information regarding symptomatic vs. asymptomatic treatment-related necrosis were available in 13 studies [12–14, 16, 25, 27–30, 32, 33, 35, 36] and the proportion of symptomatic treatment-related necrosis ranged 25–100%, and seven studies only included symptomatic treatment-related necrosis [12–14, 25, 32, 33, 35]. The median follow-up period ranged 5–31.6 months.

The treatment characteristics are summarized in Table 3. Maximum interval between SRS and ICI to define SRS+ICI combination therapy was described in seven studies, ranging from 2 to 3 days to 1 year [12, 13, 28–30, 33, 36]. Among the included studies, eight studies used only SRS [12–14, 26, 29, 30, 33, 35], and the other eight studies used also whole-brain radiation therapy or fractionated stereotactic radiotherapy for their study population [16, 25, 27, 28, 31, 32, 34, 36]. The types of ICI used were available in all except one study. Ipilimumab was only used in six studies [14, 25–27, 29, 34], and pembrolizumab was only used in two studies [30, 32]. The other six studies used two or more ICIs for their study population [12, 13, 16, 28, 35, 36].

**Table 1** Study and patient characteristics of the included studies

Author (publication year)	Institution	Multicenter	Recruitment period	Primary tumor	Analysis	No. <sup>a</sup>	Age (years)	Male:female
<b>Stereotactic radiosurgery</b>								
Knisely JP, et al (2012) [26]	Hofstra University, USA	No	11/2002–11/2010	Melanoma	Per-patient	50	59 (95% CI, 55–63)	33:17
Silk AW, et al (2013) [25]	University of Michigan Comprehensive Cancer Center, USA	No	2005–2012	Melanoma	Per-patient	22	58	20:17 <sup>b</sup>
Kaidar-Person O, et al (2017) [16]	UNC Lineberger Comprehensive Cancer Center, USA	No	2007–2015	Melanoma	Per-patient	29	62	NA
Patel KR, et al (2017) [29]	Winship Cancer Institute, USA	No	2009–2013	Melanoma	Per-patient	34	60	28:6
Diao K, et al (2018) [14]	Keck School of Medicine of USC, USA	No	2006–2015	Melanoma	Per-lesion	219	62 (IQR, 53–71)	22:7
Kotecha R, et al (2018) [31]	Taussig Cancer Institute, Cleveland Clinic, USA	No	1987–2014	Melanoma	Per-lesion	635	NA	NA
Hubbelling HG, et al (2018) [35]	Massachusetts General Hospital, USA	No	08/2013–09/2016	NSCLC	Per-patient	59	NA	NA
Shepard MJ, et al (2019) [12]	University of Virginia Health System, USA	No	01/2012–01/2018	NSCLC	Per-patient	34	64 (95% CI, 44–84)	20:14
<b>Stereotactic radiosurgery + immune checkpoint inhibitor</b>								
Knisely JP, et al (2012) [26]	Hofstra University, USA	No	11/2002–11/2010	Melanoma	Per-patient	27	53 (95% CI, 50–56)	16:11
Silk AW, et al (2013) [25]	University of Michigan Comprehensive Cancer Center, USA	No	2005–2012	Melanoma	Per-patient	22	57	20:13 <sup>b</sup>
Olson AC, et al (2016) [34]	Duke University Medical Center, USA	No	2010–2014	Melanoma	Per-patient	27	63 (range, 55–68)	14:13
Fang P, et al (2017) [36]	University of Texas MD Anderson Cancer Center, USA	No	01/2006–12/2015	Melanoma	Per-patient	137	57 (range, 16–83)	94:43
Kaidar-Person O, et al (2017) [16]	UNC Lineberger Comprehensive Cancer Center, USA	No	2007–2015	Melanoma	Per-patient	29	57	NA
Patel KR, et al (2017) [29]	Winship Cancer Institute, USA	No	2009–2013	Melanoma	Per-patient	20	57	13:7
Skrepnik T, et al (2017) [27]	University of Arizona, USA	No	2011–2015	Melanoma	Per-patient	25	69 (range, 33–85)	20:5
Diao K, et al (2018) [14]	Keck School of Medicine of USC, USA	No	2006–2015	Melanoma	Per-lesion	91	NA	27:16
Du Four S, et al (2018) [32]	Universitair Ziekenhuis Brussel, Belgium	No	09/2014–09/2016	Melanoma	Per-patient	39	50 (range, 33–84) <sup>b</sup>	14:29 <sup>b</sup>
Kotecha R, et al (2018) [31]	Taussig Cancer Institute, Cleveland Clinic, USA	No	1987–2014	Melanoma	Per-lesion	44	NA	NA
Nardin C, et al (2018) [30]	Gustave Roussy, France	No	09/2012–09/2015	Melanoma	Per-patient	25	58 (range, 32–80)	14:11
Robin TP, et al (2018) [33]	University of Colorado School of Medicine, USA	No	01/2012–08/2017	Melanoma	Per-patient	38	NA	24:14
Minniti G, et al (2019) [13]	Sant' Andrea Hospital and UPMC Hillman Cancer Center San Pietro Hospital, USA	Yes	09/2012–12/2017	Melanoma	Per-patient	80	NA	49:31
Pires da Silva I, et al (2019) [28]	Multicenter, Australia	Yes	07/2010–07/2016	Melanoma	Per-patient	135	55 (range, 16–89)	83:52
Hubbelling HG, et al (2018) [35]	Massachusetts General Hospital, USA	No	08/2013–09/2016	NSCLC	Per-patient	35	NA	NA
Shepard MJ, et al (2019) [12]	University of Virginia Health System, USA	No	01/2012–01/2018	NSCLC	Per-patient	17	64 (95% CI, 47–81)	11:6

All included studies were conducted as a retrospective fashion

NSCLC, non-small cell lung cancer; CI, confidence interval; IQR, interquartile range; NA, not available

<sup>a</sup>The number of the patients/lesions in which presence versus absence of treatment-related necrosis was evaluable

<sup>b</sup>There was a discrepancy between the number of enrolled patients and the number of patients in which presence versus absence of treatment-related necrosis was evaluable



## Quality assessment

Since all studies were conducted as a retrospective fashion, all were initially rated with a low certainty rate. In the risk of bias domain, two studies were downrated as they performed per-lesion analysis [14, 31]. In the inconsistency domain, one study was downrated because of a large difference of reported incidence compared to other studies [29]. Consequently, the quality of evidence was low in 13 [12, 13, 16, 25–28, 30, 32–36], and very low in three studies [14, 29, 31].

## Incidence of treatment-related necrosis

In melanoma brain metastasis including 14 studies [13, 14, 16, 25–34, 36], the incidences of treatment-related necrosis in SRS and SRS+ICI group were 6.5% (95% CI, 2.4–16.1%) and 16.0% (95% CI, 11.2–22.4%), respectively. In NSCLC brain metastasis including two studies [12, 35], the incidences of treatment-related necrosis in SRS and SRS+ICI group ranged 2.9–3.4% and 0–2.9%, respectively. Meta-analytic pooling was not conducted because of the small number of included studies.

Considering the difference of incidence of treatment-related necrosis and only two studies available on NSCLC brain metastasis, further analyses were performed only for 14 studies on melanoma brain metastasis. In melanoma brain metastasis, the incidence of treatment-related necrosis based on random-effects modeling was higher in the SRS+ICI group compared to SRS, with borderline significance (16.0% vs. 6.5%;  $p = 0.065$ ; OR, 2.35 [95% CI, 0.948–5.818]; Fig. 2). There was no significant publication bias noted in the SRS group ( $p = 0.918$ ), but significant publication bias was noted in the SRS+ICI group ( $p = 0.010$ ). After adjusting for publication bias using the trim and fill method, the pooled incidence of treatment-related necrosis in the SRS+ICI group increased moderately to 21.3% (95% CI, 14.8–29.6%). There was substantial heterogeneity ( $I^2 > 50\%$ ) observed in both treatment groups. The difference was not demonstrated in the direct comparison (OR, 0.84; 95% CI, 0.20–3.58;  $p = 0.816$ ; Fig. 3).

In addition, the incidences of treatment-related necrosis at the specific time points were pooled including the four studies which provided the KM curves demonstrating the cumulative incidence of treatment-related necrosis across the follow-up [16, 28, 29, 36]. All four studies assessed the incidence of treatment-related necrosis in patients with melanoma brain metastasis with the clinical and radiologic diagnosis as the reference standard. The proportion of symptomatic treatment-related necrosis ranged from 54 to 75%. The median follow-up period of four studies ranged 7.3 to 26.3 months. Consequently, cumulative incidences of treatment-related necrosis 3 and 6 months and 1, 2, and 3 years after the use of SRS+ICI in patients with melanoma brain metastasis were 3%

(95% CI, 1–6%), 6% (95% CI, 2–12%), 14% (95% CI, 8–22%), 19% (95% CI, 15–24%), and 22% (95% CI, 17–26%) (Fig. 4). The pooled incidence was slightly higher at the first year, but did not reach statistical significance compared to that at the second ( $p = 0.268$ ) or third year ( $p = 0.137$ ). One study provided the KM curves demonstrating cumulative incidence of treatment-related necrosis after SRS [29]; the 6-month cumulative incidence was not statistically different between the SRS+ICI and SRS groups (6% [95% CI, 2–12%] vs. 5.9% [95% CI, 2–21%];  $p = 0.888$ ).

## Subgroup and meta-regression analysis

The results of the subgroup and meta-regression analyses are summarized in Table 4. Of note, reference standard for treatment-related necrosis was identified as the source of heterogeneity in the SRS+ICI group. The incidence of treatment-related necrosis was significantly higher when clinical and radiologic diagnosis was used as the reference standard compared to histopathologic diagnosis as the reference standard (19.3% vs. 5.2%;  $p = 0.014$ ). When histopathologic diagnosis was used as the reference standard, the incidence of treatment-related necrosis was not statistically different between the SRS+ICI and SRS groups (5.2% vs. 2.3%;  $p = 0.408$ ). The incidence of treatment-related necrosis was higher in the SRS+ICI group when the clinical and radiologic diagnosis was used as the reference standard, but did not reach statistical significance (19.3% vs. 8.3%;  $p = 0.115$ ).

Symptomatic vs. asymptomatic treatment-related necrosis was also identified as the source of heterogeneity in the SRS+ICI group. The incidence of treatment-related necrosis was significantly lower when analysis was restricted to the studies only including symptomatic treatment-related necrosis compared to that restricted to the studies including both symptomatic and asymptomatic (8.9% vs. 27.9%;  $p < 0.001$ ). The trend was also observed in the SRS group, but did not reach statistical significance (5.5% vs. 10.1%;  $p = 0.603$ ). Publication year and method of analysis were also identified as the source of heterogeneity in the SRS+ICI group, but the higher incidence of treatment-related necrosis in the SRS+ICI group remained in each subgroup except in the subgroup using per-lesion analysis. Other covariates, including mode (SRS alone vs. SRS combined with whole brain or fractionated stereotactic radiotherapy) of SRS, were not identified as a significant source of heterogeneity.

## Discussion

This meta-analysis demonstrated that the incidence of treatment-related necrosis was higher with the borderline significance when using SRS plus ICI combination therapy than SRS therapy alone for the treatment of melanoma brain

**Table 2** Reference standard, clinicoradiologic definitions, and associated findings of treatment-related necrosis

Author (publication year)	Primary tumor	Treatment		Reference standard		Clinicoradiologic definition of treatment-related necrosis	Symptomatic treatment-related necrosis (%)	Median imaging follow-up, months	Median interval from radiation to treatment-related necrosis, months	1-year cumulative incidence of treatment-related necrosis
		SRS + ICI	SRS	Clinical and radiologic	Histopathologic					
Knisely JP, et al (2012) [26]	Melanoma	Yes	Yes	NA	NA	-	NA	12.2 (range, 2.0–72.8)	NA	NA
Silk AW, et al (2013) [25]	Melanoma	Yes	Yes	NA	NA	-	3/3 (100)	· 5.3 in SRS · 18.3 in SRS + ICI	NA	NA
Kaidar-Person O, et al (2017) [16]	Melanoma	Yes	Yes	Yes	Yes	Suspicious lesions on gadolinium-MRI with local recurrence excluded by the multidisciplinary team (pathology, imaging, clinical course)	6/8 (75)	· 21 (range, 7–51)	NA	22.5%
Patel KR, et al (2017) [29]	Melanoma	Yes	Yes	Yes	No	Newly appeared contrast enhancing mass within prior radiation fields with decreased perfusion and elevated lactate	10/17 (59)	· 7.3	NA	· 20.9% in SRS · 30.0% in SRS + ICI
Diao K, et al (2018) [14]	Melanoma	Yes	Yes	No	Yes	-	5/5 (100)	· 7.4	6.6 (range, 3.5–42)	· NA
Kotecha R, et al (2018) [31]	Melanoma	Yes	Yes	Yes	Yes	Lesions radiographically enlarged or with symptomatic change showing improvement on short-term follow-up or stable/worse but decreased perfusion and/or FDG-PET uptake	NA	· 5 (range, 1–327)	NA	· 2% (95% CI, 1–5%)
Olson AC, et al (2016) [34]	Melanoma	Yes	No	NA	Yes	-	NA	7.1 (IQR, 3.1–13.1)	NA	NA
Fang P, et al (2017) [36]	Melanoma	Yes	No	Yes	Yes	A lesion having radiographic changes with stable or improved radiographic findings with or without steroids	20/37 (54)	9.8 (range, 0–104.6)	6 (range, 1.3–31.4)	NA
Skrepnik T, et al (2017) [27]	Melanoma	Yes	No	Yes	No	Based on neuroradiology interpretation of sequential scans with perfusion imaging and multidisciplinary review	3/12 (25)	22.7	14.7 (range, 8.1–71.7)	NA
Du Four S, et al (2018) [32]	Melanoma	Yes	No	Yes	No	Based on diagnostic MRI mostly combined with perfusion and spectroscopy	5/5 (100)	50 (range, 33–84)	11.15 (range, 8–46)	NA
	Melanoma	Yes	No	Yes	No	Enhancing lesion with a central area of necrosis on T1- and	3/4 (75)	· 14 in SRS	6.5 (range, 3–10)	NA

**Table 2** (continued)

Author (publication year)	Primary tumor	Treatment		Reference standard		Clinicoradiologic definition of treatment-related necrosis	Symptomatic treatment-related necrosis (%)	Median imaging follow-up, months	Median interval from radiation to treatment-related necrosis, months	1-year cumulative incidence of treatment-related necrosis
		SRS + ICI	SRS	Clinical and radiologic	Histopathologic					
Nardin C, et al (2018) [30]						T2-weighted images, established on repeated MRI with functional scanning (i.e., increased signal intensity on follow-up, and low signal intensity on perfusion imaging)		· 8.4 (range, 1–30) in SRS + ICI		
Robin TP, et al (2018) [33]	Melanoma	Yes	No	No	Yes	-	3/3 (100)	31.6	NA	NA
Minniti G, et al (2019) [13]	Melanoma	Yes	No	Yes	No	Radiologically progressed lesion (new enhancement or enlargement) which is stable or shrunken over a 6-month observational period	12/12 (100)	15	NA	· 25% in SRS + ipilimumab · 17% in SRS + nivolumab
Pires da Silva I, et al (2019) [28]	Melanoma	Yes	No	Yes	Yes	Lesions with peripheral enhancement and central hypointensity, two consecutive MRI showing evidence of necrosis or advanced MRI and/or PET imaging suggestive of necrosis	25/36 (70)	26.3 (95% CI, 22.3–29.8)	NA	8%
Hubbeling HG, et al (2018) [35]	NSCLC	Yes	Yes	No	Yes	-	3/3 (100)	16 (range, 1–140)	NA	NA
Shepard MJ, et al (2019) [12]	NSCLC	Yes	Yes	Yes	No	Progressive volume increase on postcontrast T1-weighted images with concurrent increasing FLAIR signal changes that resolved or dramatically improved over time	1/1 (100)	· 10.4 ± 9.9 in SRS + ICI · 7.0 ± 8.4 in SRS + ICI	NA	NA

SRS, stereotactic radiosurgery; ICI, immune checkpoint inhibitor; NA, not available



**Table 3** Treatment characteristics of the included studies

Author (publication year)	Primary tumor	Interval between ICI and SRS to define SRS+ICI	Immune checkpoint inhibitor			Stereotactic radiosurgery			Gross target volume
			Drug	Dose	Timing	Mode	Dose	Fraction	
<b>Stereotactic radiosurgery</b>									
Knisely JP, et al (2012) [26]	Melanoma	-	-	-	-	SRS	NA	NA	NA
Silk AW, et al (2013) [25]	Melanoma	-	-	-	-	SRS ( <i>n</i> = 21), WBRT ( <i>n</i> = 16) <sup>a</sup>	14–24 Gy in SRS; 30–37.5 Gy in WBRT	1–5 fractions in SRS; 10–13 fractions in WBRT	NA
Kaidar-Person O, et al (2017) [16]	Melanoma	-	-	-	-	SRS ( <i>n</i> = 18), FSRT ( <i>n</i> = 11)	Median 20 Gy in SRS; 21 Gy in FSRT	NA	NA
Patel KR, et al (2017) [29]	Melanoma	-	-	-	-	SRS	NA	Single fraction	Median 2.66 cm <sup>3</sup>
Diao K, et al (2018) [14]	Melanoma	-	-	-	-	SRS	20 Gy	NA	Median 0.42 cm <sup>3</sup> (range, 0.01–21.8)
Kotecha R, et al (2018) [31]	Melanoma	-	-	-	-	SRS	NA	NA	NA
Hubbelling HG, et al (2018) [35]	NSCLC	-	-	-	-	SRS	NA	NA	NA
Shepard MJ, et al (2019) [12]	NSCLC	-	-	-	-	SRS	NA	NA	NA
<b>Stereotactic radiosurgery + immune checkpoint inhibitor</b>									
Knisely JP, et al (2012) [26]	Melanoma	NA	NA	Before RT ( <i>n</i> = 11), after RT ( <i>n</i> = 16)	Ipilimumab	NA	NA	NA	NA
Silk AW, et al (2013) [25]	Melanoma	NA	3 mg/kg every 3 weeks for a planned four doses	Before RT ( <i>n</i> = 10), after RT ( <i>n</i> = 12)	Ipilimumab	3 mg/kg every 3 weeks for a planned four doses	14–24 Gy in SRS; 30–37.5 Gy in WBRT	1–5 fractions in SRS; 10–13 fractions in WBRT	NA
Olson AC, et al (2016) [34]	Melanoma	NA	3 mg/kg every 3 weeks for a total of four doses	Before RT ( <i>n</i> = 25),	Ipilimumab	3 mg/kg every 3 weeks for a total of four doses	Median 25 Gy	NA	NA

**Table 3** (continued)

Author (publication year)	Primary tumor	Interval between ICI and SRS to define SRS+ICI	Immune checkpoint inhibitor		Stereotactic radiosurgery				
			Drug	Dose	Timing	Mode	Dose	Fraction	Gross target volume
Fang P, et al (2017) [36]	Melanoma	Within 1 year	Ipilimumab (n = 257), pembrolizumab (n = 27), ipilimumab+pembrolizumab (n = 11) <sup>b</sup>	NA	during/after RT (n = 33) <sup>b</sup> Before RT (n = 180), after RT (n = 116) <sup>b</sup>	SRS (n = 81), SRS + WBRT (n = 56)	Median 20 Gy	NA	Median 0.12 cm <sup>3</sup> (range, 0.003–25.3)
Kaidar-Person O, et al (2017) [16]	Melanoma	NA	Ipilimumab (n = 19), ipilimumab+anti-PD1 (n = 7), anti-PD1 (n = 3) <sup>c</sup>	3 mg/kg every 3 weeks for 4 doses in ipilimumab; 2 or 10 mg/kg in pembrolizumab; 3 mg/kg in nivolumab	Before RT (n = 3), after RT (n = 16), before and after RT (n = 8), concurrent and after RT (n = 1)	SRS (n = 21), FSRT (n = 8)	Median 20 Gy in SRS; 21 Gy in FSRT	NA	NA
Patel KR, et al (2017) [29]	Melanoma	Within 4 months	Ipilimumab	3 mg/kg within 4 months of SRS	NA	SRS	NA	NA	Single fraction (n = 16), multifraction (n = 4) Median 1.1 cm <sup>3</sup>
Skrepnik T, et al (2017) [27]	Melanoma	NA	Ipilimumab	Median 3 mg/kg (range, 3–10 mg/kg) every 3 weeks for a median of four cycles (range, 1–13)	Before RT (n = 9), after RT (n = 5), concurrent (n = 11)	SRS (n = 18), SRS + WBRT (n = 7)	Median 21 Gy	NA	NA
Diao K, et al (2018) [14]	Melanoma	NA	Ipilimumab	3 mg/kg (n = 36) or 10 mg/kg (n = 11) every 3 weeksd	Concurrent (n = 18), nonconcurrent (n = 26)	SRS	NA	NA	NA
Du Four S, et al (2018) [32]	Melanoma	NA	Pembrolizumab	2 mg/kg every 3 weeks	After RT (n = 28), concurrent (n = 11)	SRS (n = 31), WBRT (n = 8)	NA	NA	NA
Kotecha R, et al (2018) [31]	Melanoma	NA	NA	NA	NA	SRS or WBRT	NA	NA	NA
Nardin C, et al (2018) [30]	Melanoma	Within 6 months	Pembrolizumab	3 or 10 mg/kg every 2 or 3 weeks	Before RT (n = 21), after RT (n = 17),	SRS	NA	NA	Single fraction (n = 29), multifraction (n = 31) <sup>b</sup> Median 0.43 cm <sup>3</sup> (range, 0.05–5.3)

Table 3 (continued)

Author (publication year)	Primary tumor	Interval between ICI and SRS to define SRS+ICI	Immune checkpoint inhibitor		Dose	Timing	Stereotactic radiosurgery			
			Drug	Dose			Mode	Dose	Fraction	Gross target volume
Robin TP, et al (2018) [33]	Melanoma	Within 8 weeks	NA	NA	NA	concurrent (n = 22) <sup>b</sup>	SRS	NA	NA	NA
Minniti G, et al (2019) [13]	Melanoma	ICI administered 48–72 h before SRS	Ipilimumab (n = 45), nivolumab (n = 35)	Up to four doses of 10 mg/kg every 3 weeks, then a maintenance dose of 10 mg/kg every 12 weeks; 3 mg/kg every 2 weeks in nivolumab	NA	NA	SRS	NA	Single fraction (n = 283), multifraction (n = 41) <sup>b</sup>	NA
Pires da Silva I, et al (2019) [28]	Melanoma	Within 1 year	Anti-PD1 (n = 129), ipilimumab+anti-PD1 (n = 6) <sup>c</sup>	NA	NA	NA	SRS (n = 86), WBRT (n = 20), SRS + WBRT (n = 29)	NA	NA	NA
Hubbeling HG, et al (2018) [35]	NSCLC	NA	Nivolumab, pembrolizumab, atezolimumab	NA	NA	NA	SRS	NA	NA	NA
Shepard MJ, et al (2019) [12]	NSCLC	Within 3 months	Nivolumab, pembrolizumab, atezolimumab	NA	NA	NA	SRS	NA	NA	NA

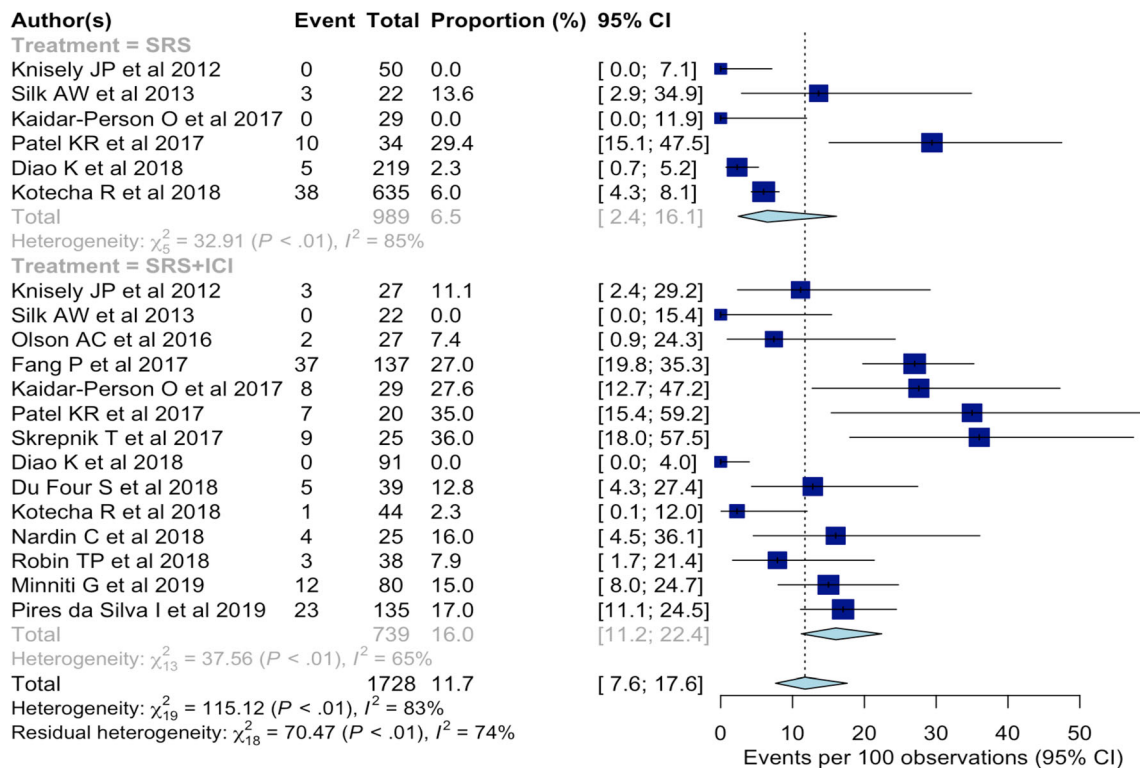
ICI, immune checkpoint inhibitor; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy; FSRT, fractionated stereotactic radiotherapy; RT, radiation therapy; anti-PD1, anti-programmed cell death protein 1; NA, not available

<sup>a</sup> There was a discrepancy between the number of enrolled patients and the number of patients in which presence versus absence of treatment-related necrosis was evaluable

<sup>b</sup> The data was reported as a per-lesion basis

<sup>c</sup> Anti-PD1 indicates pembrolizumab or nivolumab

<sup>d</sup> The data was reported as a per-patient basis



**Fig. 2** Forest plot for the incidence of the treatment-related necrosis after the use of stereotactic radiosurgery (SRS) with or without immune checkpoint inhibitor (ICI) in melanoma brain metastasis

metastases (16.0% vs. 6.5%;  $p = 0.065$ ; OR, 2.35). Treatment-related necrosis more frequently occurred with melanoma than NSCLC.

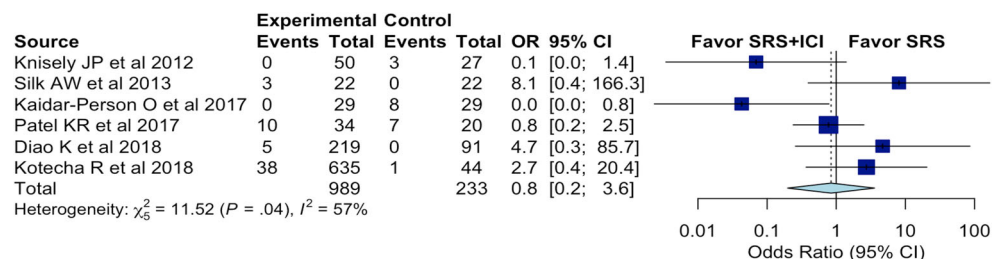
The incidence of treatment-related necrosis showed rapid increase until 12 months after the SRS treatment when combined with ICI therapy (14%; 95% CI, 8–22%) and its pace of increase slowed thereafter. In the subgroup and meta-regression analysis, the reported incidence of treatment-related necrosis was lower when histologic diagnosis was used as the reference standard compared to clinical and radiologic diagnosis and when only symptomatic treatment-related necrosis was included in the SRS+ICI group. The incidence of treatment-related necrosis in the SRS+ICI group remained higher when stratified by publication year and method of analysis, except in the subgroup using per-lesion analysis, which were identified as sources of data heterogeneity.

SRS+ICI combination therapy has been increasingly adopted since several studies demonstrated a high local

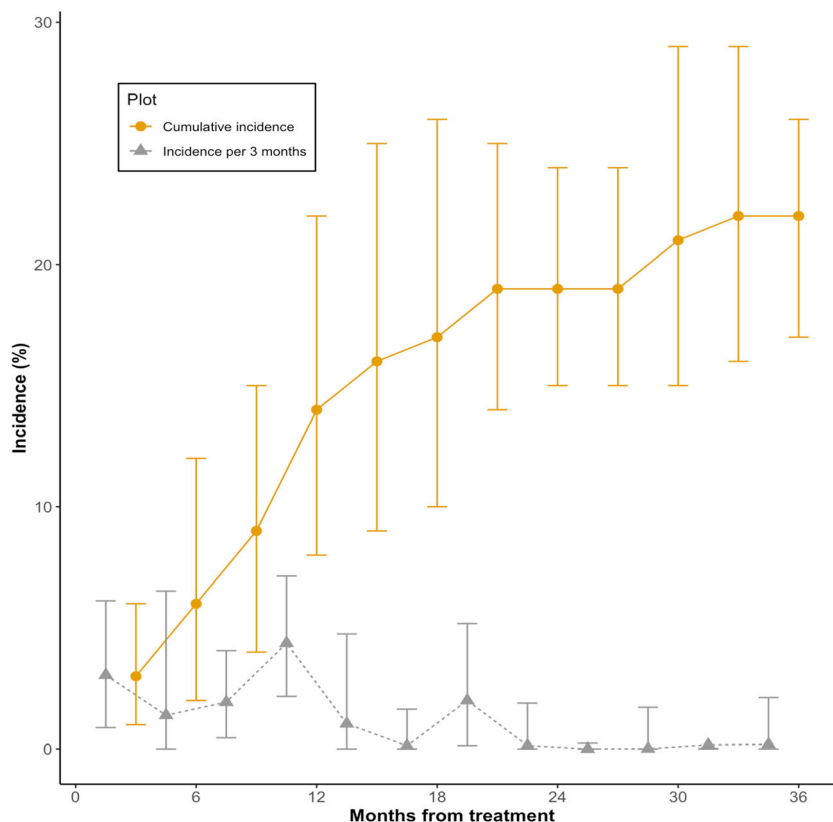
efficacy for the treatment of brain metastasis [12, 25, 30, 35, 37–39]. However, it has remained controversial whether treatment-related necrosis, one of the most important toxicities of SRS, occurs more frequently when combined with ICI therapy [40]. Our study showed that treatment-related necrosis more frequently developed in patients who received SRS+ICI therapy than in those treated with SRS alone. The higher incidence of treatment-related necrosis in the SRS+ICI group was observed in all subgroup analyses, indicating that these results are robust. This higher incidence could be explained by the hypothesis that radiation induces immune activation targeting not only tumor but also peritumoral brain tissue [41–43]. In particular, for melanoma brain metastases, treatment-related necrosis based on clinical and radiologic diagnosis developed in a considerable portion of patients, approximately 20% at the first year after the treatment.

However, it should be emphasized that diagnostic criteria of and reference standard for treatment-related necrosis varied

**Fig. 3** Forest plot for the odds ratio for the development of treatment-related necrosis after the use of stereotactic radiosurgery (SRS) with immune checkpoint inhibitor (ICI) compared to SRS in melanoma brain metastasis



**Fig. 4** The pooled cumulative incidence and incidence per 3 months of treatment-related necrosis after the stereotactic radiosurgery with immune checkpoint inhibitor for the treatment of melanoma brain metastasis across the follow-up period. Error bars represent 95% confidence interval



across the studies. Moreover, the studies varied on whether asymptomatic necrosis was included. These two factors may be correlated because symptomatic treatment-related necrosis requires further treatment such as surgery; thus, there may be a bias toward having histopathological confirmation in patients with symptomatic treatment-related necrosis. While histopathologic diagnosis is the gold standard for the diagnosis of treatment-related necrosis, brain biopsy and surgery are non-trivial, and it is thus somewhat inevitable and clinically necessary to define treatment-related necrosis with clinical and radiologic information. However, in that setting, it is difficult to differentiate treatment-related necrosis from true tumor progression [44]. The RANO brain metastasis working group recommends follow-up imaging 4 to 6 weeks after assessment in equivocal cases following SRS [45] and follow-up imaging at 3-month intervals during immunotherapy [46, 47]. The majority of the included studies utilized this follow-up strategy, but the exact follow-up period was often unreported. Furthermore, some studies used advanced imaging and/or FDG-PET for the diagnosis, but some studies did not. There is currently no specific clinicrodiologic criteria for the diagnosis of treatment-related necrosis in the setting of SRS+ICI combination therapy. Standards should be developed to improve clinical practice and focus future research.

In this context, issues regarding pseudoprogression should be further discussed. Treatment-related necrosis

refers to a late-delayed necrosis as a consequence of radiation with or without chemotherapy, characterized by irreversible damage to blood vessels leading to ischemic necrosis, demyelination, and hemorrhage [44, 48]. In contrast, pseudoprogression refers to a unique, transient, predominantly radiologic phenomenon after the treatment, usually used in patients with gliomas especially within 3 months after the treatment [44]. Advanced MR techniques such as spectroscopy, perfusion imaging, and amino acid PET have been reported to be helpful for discriminating pseudoprogression and true progression [49, 50]. Recently, pseudoprogression is also used to indicate the radiologic change of other cancers after immunotherapy [51]. The pooled incidence of pseudoprogression seems to be much higher in patients with glioblastoma (36%; 95% CI, 33–40%) [52] than in patients with metastasis from other solid tumors (6%; 95% CI, 5–7%) [53]. Indeed, pseudoprogression as a consequence of ICI therapy in the early time frame of treatment might be misinterpreted to be treatment-related necrosis leading to a bias, but discrimination between pseudoprogression and treatment-related necrosis was not clear in the included studies, which remains to be a diagnostic challenge.

In this meta-analysis, the incidence of treatment-related necrosis was much higher in melanoma than NSCLC. This finding might be due to the small number of NSCLC studies



**Table 4.** Summary of subgroup and meta-regression analysis

Covariate	Stereotactic radiosurgery			Stereotactic radiosurgery + immune checkpoint inhibitor			<i>p</i> value <sup>b</sup>
	No. of studies	% (95% CI)	<i>p</i> value <sup>a</sup>	No. of studies	% (95% CI)	<i>p</i> value <sup>a</sup>	
Publication year							
< 2018	4	8.8 (2.1–30.5)	0.247	7	23.1 (15.2–33.3)	0.026	0.278
≥ 2018	2	4.0 (1.6–10.0)		7	11.7 (7.4–18.1)		0.028
Analysis							
Per-patient	4	8.8 (2.1–30.5)	0.247	12	18.6 (13.8–24.7)	0.002	0.528
Per-lesion	2	4.0 (1.6–10.0)		2	1.4 (0.3–6.7)		0.271
Reference standard for treatment-related necrosis							
Histopathologic diagnosis	1	2.3 (1.0–5.4)	0.311	3	5.2 (1.6–15.5)	0.014	0.408
Clinical and radiologic diagnosis	5	8.3 (2.7–22.6)		11	19.3 (14.0–26.0)		0.115
Symptomatic treatment-related necrosis only included							
Yes	2	5.5 (0.9–27.3)	0.603	5	8.9 (4.2–17.7)	< 0.001	0.586
No	2	10.1 (0.5–71.2)		5	27.9 (22.5–34.0)		0.615
Immune checkpoint inhibitor used							
Ipilimumab only	0	-	-	6	12.7 (2.9–41.2)	0.752	-
Others	6	6.5 (2.4–16.1)		8	18.3 (12.4–26.0)		0.066
Mode of SRS							
SRS alone	4	6.1 (1.8–19.1)	0.921	6	13.4 (6.9–24.2)	0.507	0.320
SRS combined with WBRT/FSRT	2	7.0 (0.9–37.1)		8	17.9 (11.5–26.8)		0.291

CI, confidence interval; WBRT, whole-brain radiation therapy; FSRT, fractionated stereotactic radiotherapy

<sup>a</sup>*p* value indicates the statistical difference between the two categories within each treatment group

<sup>b</sup>*p* value indicates the statistical difference between the two treatment groups within the same categories

included, which may have led to inaccuracy of the pooled estimate. However, the possibility of an intrinsic difference in the sensitivity to radiation and/or ICI therapy between melanoma and NSCLC cannot be excluded and has been previously reported with a treatment-related necrosis hazard ratio in melanoma of 4.02 and in NSCLC of 2.56 compared also with renal cell carcinoma [15]. Indeed, melanoma has been known to be radioresistant thereby requiring a higher radiation dose to control [54]. Although it was not possible to compare radiation dose between NSCLC and melanoma brain metastasis in our study because information regarding radiation dose was not reported in two studies on NSCLC, it might be assumed that a higher radiation dose might be prescribed during SRS for treating melanoma brain metastasis, and this also could be a reason to explain the difference of the incidence between melanoma and NSCLC.

There are several notable limitations to this study. First, all included studies were retrospective and assessment time for the diagnosis of treatment-related necrosis was not clear in most of the studies. Second, definitions of treatment-related necrosis and follow-up time were inconsistent across the included studies. Furthermore, only two studies specified in the definition that the location of the treatment-related necrosis

was the same location previously irradiated. These would impose the risk of inaccuracy of the pooled estimates. Third, the number of included studies is modest, and in particular, there were only eight studies providing information for the direct comparison. Fourth, multicollinearity between the identified sources of heterogeneity could not be assessed based on the study-level data. Fifth, it was not possible to evaluate the association between the development of treatment-related necrosis and what and how ICI was used (e.g., monotherapy vs. combination therapy, ipilimumab vs. nivolumab vs. pembrolizumab). Finally, we could not perform meta-regression analysis to evaluate whether the timing in regard to ICI (before SRS vs. after SRS vs. concurrent use), mode, and radiation fractions of SRS would be the source of heterogeneity. Further studies are required to clarify this issue.

In conclusion, treatment-related necrosis tended to occur 2.4 times more frequently in the setting of SRS+ICI combination therapy compared with SRS alone in melanoma brain metastasis showing high cumulative incidence within the first year. Treatment-related necrosis should be considered when SRS+ICI therapy combination is used for melanoma brain metastasis, especially in the first year.

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## Compliance with ethical standards

**Guarantor** The scientific guarantor of this publication is Chong Hyun Suh.

**Conflict of interest** The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

**Statistics and biometry** No complex statistical methods were necessary for this paper.

**Informed consent** Written informed consent was not required for this study because this study is a systematic review and meta-analysis.

**Ethical approval** Ethical approval was not required for this study because this study is a systematic review and meta-analysis.

## Methodology

- Meta-analysis
- Performed at one institution

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