Critical Reviews in Oncology / Hematology 144 (2019) 102830

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Combination of radiotherapy and immunotherapy for brain metastases: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Brain metastases
Radiotherapy
Immunotherapy
Survival
Meta-analysis

ABSTRACT

Radiotherapy (RT) represents a mainstay in the treatment of brain metastases (BMs) from solid tumors. Immunotherapy (IT) has improved survival of metastatic cancer patients across many tumor types. The combination of RT and IT for the treatment of BMs has a strong rationale, but data on efficacy and safety of this combination is still limited. A systematic search of PubMed, the Cochrane Central Register of Controlled Trials, and EMBASE was conducted.

33 studies were included for a total of 1520 patients, most of them with melanoma (87%). Median pooled OS was 15.9 months (95%CI 13.9–18.1). One- and 2-year OS rates were 55.2% (95% CI 49.3–60.9) and 35.7% (95% CI 30.4–41.3), respectively. Addition of IT to RT was associated with improved OS (HR = 0.54, 95%CI 0.44-0.67; P < 0.001). For patients with BMs from solid tumors, addition of concurrent IT to brain RT is able to increase survival and provide long term control.

1. Introduction

The development of brain metastases (BMs) represents a frequent event in the natural history of several solid tumors and it is generally associated with poor prognosis in most cases due to intracranial progression of disease, with few months of median overall survival (OS) despite active treatments. The majority of BMs originate from lung cancer, breast cancer, melanoma and renal cell carcinoma (RCC) (Tabouret et al., 2012). Particularly melanoma has high propensity to metastasize to the brain, being associated with the highest incidence proportion of BMs when compared with the other primary tumors (Barnholtz-Sloan et al., 2004; Bafaloukos and Gogas, 2004). The management of BMs consists of a multimodal approach including local treatments such as surgery and/or radiotherapy (RT), systemic therapy, and symptomatic therapy (Soffietti et al., 2017). RT, in the form of whole brain radiotherapy (WBRT) and stereotactic radiotherapy (SRT), is considered a mainstay in the treatment of BMs (Tsao et al., 2018; Mulvenna et al., 2016; Yamamoto et al., 2014).

Conversely, systemic therapy for BMs has been neglected for years due to the prevailing belief that anticancer drugs do not cross the blood-brain barrier (BBB). Over the last decade, the advent of novel systemic therapies has revolutionized the systemic therapy for several malignancies. Particularly modern immunotherapy (IT), in the form of monoclonal antibodies targeting the immune checkpoint pathways (PD-1/PD-L1 and CTLA-4), have improved OS of patients with many advanced tumors such as melanoma, NSCLC and RCC, that are frequently associated with the development of BMs (Marconcini et al., 2018; Assi et al., 2018; Motzer et al., 2018). Of note, IT can achieve long-lasting benefit, with 20–30% of long-term survivors across different tumor types (Gettinger et al., 2018; Maio et al., 2015).

Indeed, data on the efficacy of IT against BMs is limited, since patients with BMs were generally excluded from pivotal IT trials or they were included only whether BMs were stable or asymptomatic. The early analysis of a phase 2 trial on 52 patients with untreated BMs from melanoma or NSCLC receiving the anti-PD-1 antibody pembrolizumab reported promising activity (with a RR of 22% and 33% for the

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https://doi.org/10.1016/j.critrevonc.2019.102830
Received 22 September 2018; Received in revised form 15 June 2019; Accepted 26 October 2019
1040-8428/

melanoma and NSCLC cohorts, respectively), with an acceptable safety profile (Goldberg et al., 2016a). A phase 2 randomized study compared the anti PD-1 antibody nivolumab alone with the combination of nivolumab plus the anti-CTLA-4 antibody ipilimumab in patients with BMs from melanoma (Long et al., 2018). Among 63 patients with previously untreated BMs, intracranial responses were observed in 20% and 46% of patients treated with nivolumab and with nivolumab plus ipilimumab, respectively (Long et al., 2018).

Based on this background, there is a strong rationale for combining RT and IT, and this is further supported by preclinical evidence. In fact, RT may locally interact with the immune system inducing production of inflammatory cytokines, release of tumor antigens and inhibition of immune suppressive cells, thus enhancing the activity of IT (Demaria et al., 2005). Additional reports indicate that the PD-1 ligand, PD-L1, could be upregulated in the tumour microenvironment following radiotherapy, which could result from an extrinsic effect of local cytokine release or through an intrinsic p53-mediated mechanism (Cortez et al., 2016; Spitzer et al., 2016). In fact, there is growing preclinical data suggesting a synergistic effect for RT given with IT in terms of enhanced response rates, not only at the irradiated target but also at distant sites (abscopal effect) (Park et al., 2015). RT may also alter the blood-brain barrier (BBB) functions thus allowing for the penetration of IT drugs and effector immune cells into BMs (van Vulpen et al., 2002).

Although the optimal combination of IT and RT to the brain in terms of dose, fractionation and timing has not yet established, several retrospective series suggested that combining IT and RT for the treatment of BMs from melanoma and other primary tumors may represent a safe strategy with promising activity (Khalifa et al., 2016; Franceschini et al., 2016). However, safety and efficacy in terms of local control and OS of IT given with brain RT has not been fully clarified.

We performed a systematic review of the literature reporting outcomes and toxicity of patients with solid tumors treated with IT and RT for BMs.

2. Materials and methods

2.1. Study search and inclusion criteria

This systematic review has been conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Moher et al., 2009).

Databases such as PubMed, Embase, and the Cochrane library were used for the literature search using the following keywords: *(PD-1[All Fields] OR pd-l1[All Fields] OR ("immunotherapy"[MeSH Terms] OR "immunotherapy"[All Fields]) OR ("ctla-4 antigen"[MeSH Terms] OR ("ctla-4″[All Fields] AND "antigen"[All Fields]) OR "ctla-4 antigen"[All Fields] OR "ctla 4″[All Fields])) AND (("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms]) OR "radiation therapy"[All Fields] OR ("radiosurgery"[MeSH Terms] OR "radiosurgery"[All Fields])) AND ("brain metastases"[All Fields] OR "central nervous system metastases"[All Fields])*. The search was performed up to 25th April 2018, without date limitation.

Candidate articles were first screened and then scrutinized independently by the two investigators (FP and AD). When discrepancies occurred during the study selection process, they were resolved by discussion with a third author (AG) between the two investigators.

2.2. Inclusion criteria

Any prospective trial or retrospective series that evaluated the efficacy and safety of RT, with any technique (WBRT or SRT), for BMs in at least ten adult patients with solid tumors treated with IT were included. Non-English written articles, conference abstracts, and studies including any investigational agent were not allowed. Duplicate use of the same study was checked and avoided. The quality of original studies was assessed using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies after arranging it for a single-arm study design (Wells et al., 2015). Studies with a rating of 7 or higher were considered high quality.

The following efficacy outcomes were analysed: median OS and 1- and 2-year OS (primary endpoints), 1- and 2-year local control, response rate (ORR), toxicity (secondary endpoints). The number of these adverse events was counted and analysed in a patient-based manner.

2.3. Data extraction

Data for the included studies were extracted by five investigators (CP, FP, AG, FT and AD) independently, and included the following: author name, publication year, and numbers of patients. Data related to the study outcomes were also extracted, such as OS (median 1- and 2-year), local control and adverse events, number and size of BMs, line of therapy, type and dose of RT, and systemic agent. The data extracted by the 3 investigators were cross-checked, and any discrepancies were discussed between them. OS was defined the time elapsed from start of local or systemic treatment (or from diagnosis of BMs if it is the same of the start of RT) whichever came first to any death.

2.4. Statistical analysis

Binary data were meta-analysed with the random-model generic inverse variance method. Median OS was pooled using weight calculated from the 95% confidence interval (95% CI) and sample size. When available from text or calculated from survival curves, hazard ratios for OS, comparing addition of IT to RT alone, were aggregated in a formal meta-analysis according to fixed or random effect model. The heterogeneity was assessed using I^2 statistics with P values of < 0.05 or I^2 values of $> 50\%$ being considered to be significant. An appropriate statistical model (fixed or random-effects model) was used to pool the percentages and corresponding 95% confidence intervals (CIs) based on the results of the heterogeneity test. For all of these analyses, P values of < 0.05 indicated statistical significance. Publication bias was checked with Begg's and Egger's test for primary endpoints (Begg and Mazumdar, 1994; Egger et al., 1997). All analyses were performed in Comprehensive Meta-analysis v 3.3.070.

3. Results

After the electronic search a total of 305 paper were retrieved. A flow diagram for the study is shown in Fig. 1. Reading the titles and abstracts led to exclusion of 268 papers because they were not pertinent or were duplicates. Among the remaining 37 publications, 33 trials (Acharya et al., 2017; Ahmed et al., 2017; An et al., 2017; Anderson et al., 2017; Chen et al., 2018; Choong et al., 2017; Diao et al., 2018; Fang et al., 2017; Gaudy-Marqueste et al., 2017; Gerber, 2015; Medsker et al., 2016; Hubbeling et al., 2018; Kaidar-Person et al., 2017; Kiess et al., 2015; Knisely et al., 2012; Kotecha et al., 2017; Liniker et al., 2016; Mathew et al., 2013; Nardin et al., 2018; Olson et al., 2016; Parakh et al., 2017; Patel et al., 2017; Pike et al., 2017; Warren et al., 2017; Qian, 2016; Qin et al., 2016; Rahman et al., 2018; Schapira et al., 2018; Silk et al., 2013; Skrepnik et al., 2017; Stokes et al., 2017; Tazi et al., 2015; Theurich et al., 2016; Williams et al., 2017; Yusuf et al., 2017) consisting of 32 retrospective studies and 1 phase 1 study with 1520 patients, were entered into our meta-analysis (Table 1). These series consisted in patients with melanoma (n = 28), non-small cell lung cancer (NSCLC) (n = 3), and mixed series including melanoma, NSCLC and renal cell carcinoma (RCC) patients (n = 2). In studies with data available (n = 11), line of treatment was in almost all cases early lines (second or third). In 1 study, 21% and 6% of patients were not pretreated or heavily pretreated respectively. All studies but 6 were conducted in United States. Drugs used were ipilimumab in n = 14 studies, pembrolizumab in n = 2 studies and both anti-PD-1 or anti-CTLA-4 in n = 16 studies. In 1 publication systemic agents were not

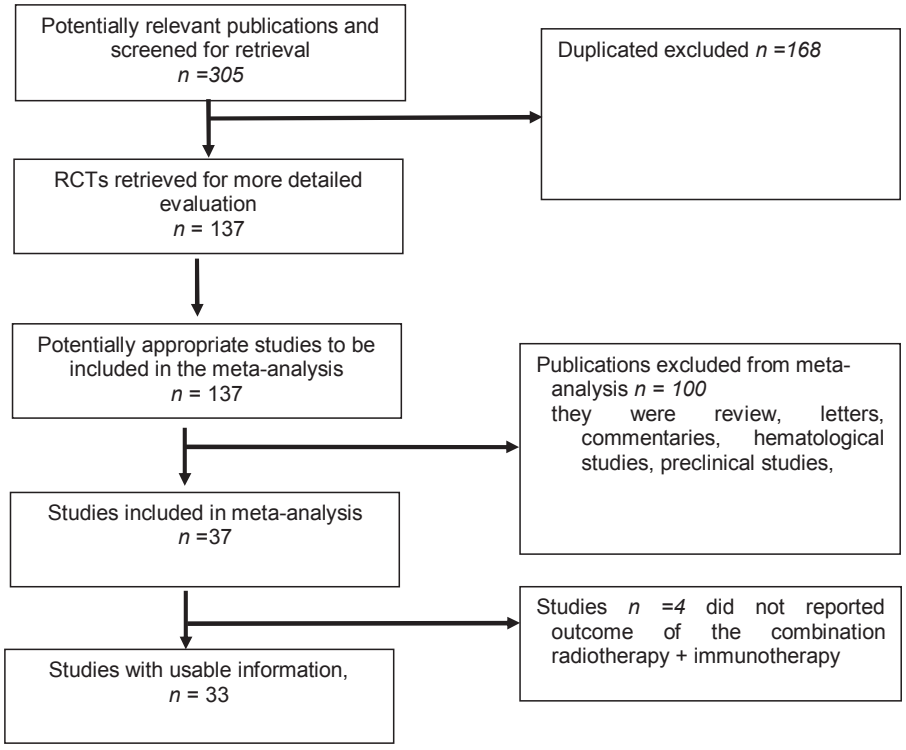

Fig. 1. Overview of trials search and selection.

specified. RT included SRT or stereotactic radiosurgery in n = 19 series, WBRT in n = 1 and both SRT and WBRT in the remaining publications. RT was given before IT in 23–100% in n = 19 studies, concurrently with IT in 5–100% of cases in n = 16 studies, and after IT in 26–100% of cases in n = 15 studies.

3.1. Overall survival and 1- and 2-year OS

The pooled median OS from start of treatment (either RT or IT) was 15.9 months (95%CI 13.9–18.1). Heterogeneity was low (I^2 = 16.7%). Data was available from n = 28 studies (n = 1295 patients). In 5 publication OS was calculated from diagnosis of BMs instead that from start of RT or IT. After excluding lung cancer or mixed series with data available (n = 4), median pooled OS for melanoma BMs was 14.4 months (95%CI 12.4–16.8). The corresponding value was 17.7 months (95%CI 9.7–30.2) for lung cancer series.

We were able to obtain data for the 1-year OS rate from n = 23 studies (n = 1252 patients). The pooled 1-year OS rate was 55.2% (95% CI 49.3–60.9) with the random effects model (heterogeneity analysis: Q = 69.3, P < 0.001, I^2 = 68%). Data from n = 22 studies (n = 1126 patients) showed a 2-year OS rate of 35.7% (95% CI 30.4–41.3) using the random effects model (heterogeneity analysis: Q = 60.6, P < 0.001, I^2 = 65.3%). Corresponding data of 1- and 2- year OS for melanoma and lung cancer patients were 54.2 (95%CI 48–60.4), 52.3% (95%CI 39.1–65.2), and 35.9 (95%CI 30.1–42.2) and 29% (95%CI 16.7–45.4) respectively.

3.2. 1- and 2-year local control

Local control at 1-year was 48% in n = 13 studies (n = 523 patients) with data available (95%CI 32.9–63.8). Data was calculated according to random effects model due to high heterogeneity (Q = 113.5, P < 0.001, I^2 = 89.4%). Local control at 2-year was 31.6% in n = 6 studies (n = 281 patients) with data available (95%CI 14.7–55.4). Data was calculated according to random effect model due to high heterogeneity (Q = 49.5, P < 0.001, I^2 = 89.9%).

3.3. Meta-analysis of RT + IT vs RT alone

The combination of RT and IT vs RT alone is showed in Fig.2. The relative benefit in OS of receiving IT during or before/after RT was significant (HR = 0.54; 95%CI 0.44–0.67) and was obtained in n = 13 studies (n = 754 patients). The effect on OS of the sequencing of RT and IT was provided by n = 15 authors. A significant benefit of RT given before/concurrently and after IT compared with the reverse sequences was observed in n = 10 and n = 1 publications, respectively. In n = 4 publications no effect of the sequencing of RT and IT was observed.

3.4. Response rate

Data about response rate of BMs was available in n = 10 studies (n = 363 patients). Criteria for evaluation of response and timing were different between studies. They ranged from 4 to 76% (median pooled 32%).

3.5. Toxicity

The analysis of G3-4 toxicity was described in 22 of 33 studies (n = 858 patients). Fatigue was reported in n = 1 study (11%). Dermatologic toxicity were dermatitis 7–48%, cutaneous rash 10% and Stevens-Johnson syndrome 5%. The negative impact of radiotherapy on CNS led to cognitive changes in 5–41% of cases, bleeding in 18–28%, radionecrosis 1–27.6%, headache 4–26%, and ataxia 4.2%. Finally were reported gastrointestinal effects like diarrhoea (10–31%), nausea (5–9%) and anorexia (4–5%).

3.6. Publication bias

Both Begg's and Egger's test were significant for potential publication bias for median OS pooled analysis (P = 0.01 for both tests). Conversely, for pooled 1- and 2-year OS both tests were not significant (Table 2).

Table 1
Characteristics of included studies.

Author/year	Type of study	Country	N° pts RT + IT	Median age	Primary tumor	N° BMs (%)	Size (median)	Line of treatment	Median OS (months) from RT	1-2 year OS (%)	1-2 year LC (%)	ORR BMs (%)
Acharya et al. (2017)	Retrospective	US	18	61	Melanoma	–	20 mm	2	14 (HR = 0.38, 0.17-0.86*; UVA)	58-NR	60-NR	–
Ahmed et al. (2017)	Retrospective	US	17	60	NSCLC	–	–	2	17.9**	53-NR	–	–
An et al. (2017)	Retrospective	US	99	62	Melanoma	2	1.45 cm	1	12.5 (HR = 0.53, 0.21-1.3; UVA)	47–21	25–16	–
Anderson et al. (2017)	Retrospective	US	21	67	Melanoma	1.5	10 mm	1	–	–	–	32
Chen et al. (2018)	Retrospective	US	79	< 70	NSCLC (n = 37), Melanoma (n = 35), Kidney (n = 7)	2	–	1	19.6** (HR = 0.37, 0.19-0.7*; MVA)	73–37	84-NR	–
Choong et al. (2017)	Retrospective	Australia	39	64	Melanoma	2	–	1	13.9 (HR = 0.51, 0.25-1.05; UVA)	56-34	–	–
Diao et al. (2018)	Retrospective	US	59	61	Melanoma	–	–	1	–	–	–	76
Fang et al. (2017)	Retrospective	US	137	57	melanoma	–	12 mm	–	16.9	75-45	–	–
Gaudy-Marqueste et al. (2017)	Retrospective	France	56	54.3	Melanoma	1:30.3%; > 3:43.5	–	–	10.7 (HR = 0.13, 0.04-0.39*; MVA)	57-43	–	–
Gerber et al. (2015)	Retrospective	US	13	64	melanoma	–	–	–	4	15.4-NR	–	11 (mWHO)
Hubbeling et al. (2018)	Retrospective	US	50	61	NSCLC	1: 60; > 3:40	13 mm.	2 (median)	–	–	–	–
Kaidar-Person et al. (2017)	Retrospective	US	29	57	melanoma	–	15 mm	–	15 (HR = 0.34, 0.19-0.6*; MVA)	66–28	28-16	–
Kiess et al. (2015)	Retrospective	US	46	57	melanoma	–	8 mm	–	12.4**	53.6-NR	8-NR	75
Knisely et al. (2012)	Retrospective	US	27	53.2	melanoma	–	–	–	21.3 (HR = 0.61, 0.33–1.1; MVA)	72–47.2	–	–
Kotecha et al. (2017)	Retrospective	US	32	57	melanoma	1:34%; > 3: 34%	9 mm	–	-(HR = 0.67, 0.44–0.99*; MVA)	24-NR	–	–
Liniker et al. (2016)	retrospective	Australia	27	63	Melanoma	7 (median)	–	–	–	–	–	33
Mathew et al. (2013)	retrospective	US	25	62	Melanoma	> 1 84; > 4 24	< 3 cm	–	5.9 (HR = 0.73, 0-41-1.3; UVA)	33–18	40–40	–
Nardin et al. (2018)	retrospective	France	25	58	Melanoma	–	16mm	–	11	49–30	–	36
Olson et al. (2016)	retrospective	US	26	63	Melanoma	–	–	–	10.4	–	44-NR	–
Parakh et al. (2017)	retrospective	Australia	66	62	Melanoma	1:10; 2-4: 52; > 4:38	23.5 mm	0:21; 1:50; 2:23; ≥3:6	9.9 § (from IT)	50–20	25–15	29
Patel et al. (2017)	retrospective	US	20	56.5	Melanoma	1-3: 90; ≥3: 10	–	–	- (HR = 1.07)	37.1–30	71.4-NR	–
Pike et al. (2017)	Retrospective	US/Canada	85	63	NSCLC (n = 39), Melanoma (n = 41), RCC (n = 5)	–	–	–	25.7 (from IT)	–	–	–
Qian et al. (2016)	Retrospective	US	75	62.5	Melanoma	–	–	–	18.5	57–32	–	–
Qin et al. (2016)	Retrospective	US	44	58	Melanoma	–	–	2	17.9 (from IT) (HR = 1.36, 0.72–2.57)	66–48	–	64.5 (@ 6 months)
Rahman et al. (2018)	Retrospective	US	35	66.7	Melanoma	2 (median)	9 mm.	–	13.9	62–54	38-NR	–
Schapira et al. (2018)	Retrospective	US	37	63	NSCLC	–	6 mm	–	17.6	52–29	86-86	–
Silk et al. (2013)	Retrospective	US	33	56.6	Melanoma	1-3: 45; > 3:55	–	–	18.3 (from IT) (HR = 0.43, 0.24–0.76*; UVA)	65–37	–	27 (n = 22)
Skrepnik et al. (2017)	Prospective	US	25	68.5	Melanoma	–	–	–	35.8	83–64	50-30 (TTP_{SNC})	4
Stokes et al. (2017)	Retrospective	US	185	–	Melanoma	–	–	–	10.8** (HR = 0.57, 0.47-0.7; MVA*)	47–28	–	–
Tazi et al. (2015)	Retrospective	US	10	65.5	Melanoma	–	–	2: 50; 1:50	16.5**	70–50	–	–
Theurich et al. (2016)	Retrospective	Germany + Swiss	46	62.1	Melanoma	–	–	–	2.8 (from IT)	42–0	–	–
Williams et al. (2017)	Phase 1	US	16	60	Melanoma	2 & 6 (median in SRS & WBRT)	–	–	8 & not reached in WBRT & SRS	55–55	–	7 (n = 15) irRC

(*continued on next page*)

Table 1 (*continued*)

Author/year	Type of study	Country	N° pts RT + IT	Median age	Primary tumor	N° BMs (%)	Size (median)	Line of treatment	Median OS (months) from RT	1-2 year OS (%)	1-2 year LC (%)	ORR BMs (%)
Yusuf et al. (2016)	Retrospective	US	18	63.8	Melanoma	–	7.9 mm	–	7.4 (HR = 0.69, 0.36-1.31; UVA)	37.5–37.5	75-NR	–

*, Statistically significant; °, group A and B respectively; irRC; immune-related response criteria; NR, not reported; § all patients treated with radiotherapy or not; **, from brain metastases diagnosis; UVA, univariate analysis; MVA, multivariate analysis, US, United States; HR, hazard ratio; BM, brain metastases; WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery; TTP_{SNC}, time to brain progression; RT, radiotherapy; IT, immunotherapy; OS, overall survival; LC, local control; ORR, overall response rate.

4. Discussion

There is a strong preclinical and clinical rationale for combining RT with IT for the treatment of BMs, with the aim to achieve both local and extracranial disease control, possibly leading to an improvement of OS. However, safety and efficacy data on this strategy are still limited.

We have performed a systematic review of studies exploring efficacy and safety of RT associated with IT for the treatment of BMs. To our knowledge, this is the first systematic review and meta-analysis explicitly assessing this topic. However, publications included in this systematic review reported mostly data of patients with BMs from melanoma (87%) and NSCLC (11%), therefore the results cannot be directly translated to patients with other primary tumors.

We found 4 main key results: prolonged OS with the combination of the 2 modalities, a good local control that strictly correlates with OS, an effect of timing of this association, and finally a survival benefit of adding IT to RT compared to RT alone. Overall, a median OS of about 16 months from initiation of any treatment was observed. Survival and local control at 1 and 2 years were strictly correlated (55 and 48%, 35 and 31% at 1- and 2- year respectively). The most compelling data was on the effect of addition of IT to RT available in n = 13 studies, that was associated to approximately 50% reduction of risk of death. Finally, the sequencing of RT and IT seems important, with RT given before or concurrently to IT providing the best effect on outcome.

In this meta-analysis the median OS of 16 months favorably compares with that previously reported of approximately 7 months for patients receiving RT with or without systemic therapy for BMs from melanoma and NSCLC (Goldberg et al., 2016b). It should be emphasized, however, that prognosis of patients with BMs is widely heterogeneous and highly depends on several prognostic factors, including both clinical and molecular variables. Despite PD-L1 expression was not systematically searched in clinical trials, activity of IT toward BMs (even if poor) seems consistent with other site of disease. In a phase 2 study with pembrolizumab in patients with lung or melanoma BM, overall response of intracranial disease was 18 and 33% (lung tumors only were requested to be PD-L1 positive) (Goldberg et al., 2016b). An updated analysis of CheckMate 204 (nivolumab + ipilimumab) with 94 enrolled patients showed a 52% BMs response rate (Tawbi et al., 2018). Systemic response was 47%, concordant with BMs responses. It appears that the response of BMs to immunotherapy is nearly similar to extracranial disease provided the primary tumor is PD-L1 positive. In another study, a strong correlation of PD-L1 expression between primary lung cancers and their corresponding BMs (not significantly influenced by chemotherapy or steroid therapy), was found (Téglási et al., 2019). Even if some cases of BMs have a discordant/lack PD-L1 expression respect to primary tumours, PD-L1 may retain the same prognostic/predictive effect in BMs and primary tumor. Infact, other authors infact found a shorter local control in PD-L1 positive BMs compared to negative cases (Takamori et al., 2018).

Different prognostic models have been developed (Sperduto et al., 2012; Gaspar et al., 1997; Sperduto et al., 2008). Among them, the disease specific grading prognostic assessment (DS-GPA) is considered the least subjective, most quantitative, and based on the most current data from randomized trials (Sperduto et al., 2012). The most recent version of DS-GPA for melanoma (Melanoma-molGPA) identified 5 significant prognostic factors for survival (age, Karnofsky performance status, extracranial metastases, number of brain metastases, and *BRAF* status), with median OS ranging from 4.9 months for the worst to 34.1 months for the best prognostic group (Sperduto et al., 2017a). Similarly, the most recent version of DS-GPA for lung cancer (Lung-molGPA) identified 6 significant prognostic factors for survival (age, Karnofsky performance status, extracranial metastases, number of brain metastases, *EGFR* and *ALK* status), with median OS ranging from 5.3 months for the worst to 46.8 months for the best prognostic group (Sperduto et al., 2017b).

In particular, the presence of targetable driver molecular alterations

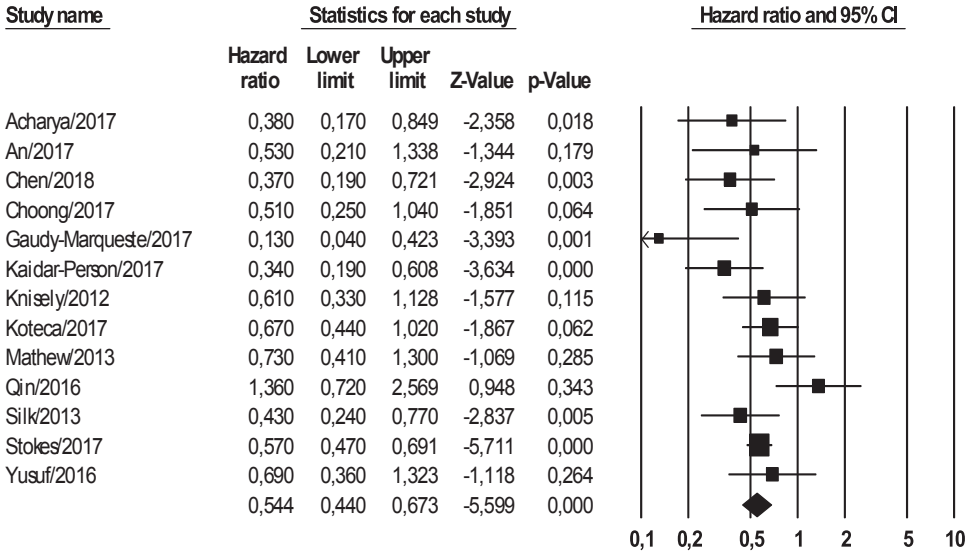

Fig. 2. Effect of addition of immunotherapy to radiotherapy compared to radiotherapy alone on overall survival.

clearly represents a strong positive prognostic factor for patients with BMs from melanoma or NSCLC. *BRAF* mutations are present in ≤50% of metastatic melanoma. In small studies on patients with BMs from melanoma harboring *BRAF* mutations, the combination of RT and BRAF inhibitors +/- MEK inhibitors demonstrated interesting activity resulting in median OS times ranging from 6 to 20 months, suggesting that the combination of RT with target therapy may be beneficial in this setting (Chowdhary et al., 2016). In a phase 3 study comparing nivolumab plus ipilimumab versus nivolumab alone versus ipilimumab alone, however, in the subgroup of patients with *BRAF* mutations median OS was not reached for the nivolumab plus ipilimumab and the nivolumab monotherapy group, after a minimum follow-up of 36 months (Wolchok et al., 2017). This cross-trials comparison suggests that in patients with *BRAF*-mutant melanoma, IT could result in better survival than target therapy, at least in asymptomatic and / or oligometastatic cases. Its combination with RT may therefore represent a valuable strategy not only for BMs from *BRAF* wild type melanoma, but also for BMs from with *BRAF*-mutated melanoma. *EGFR* mutations and *ALK* alterations are present in approximately 15–20% and 3–5% of non-squamous NSCLC, respectively. For metastatic NSCLC with driver mutations, target therapy is the standard of care. Later generation tyrosine-kinase inhibitors of EGFR and ALK have impressive activity against BMs, even when given without RT (Goss et al., 2018; Soria et al., 2018; Peters et al., 2017). In randomized clinical trials, IT demonstrated limited activity for patients with oncogene-addicted NSCLC (Bylicki et al., 2017). However, given that patients with targetable mutations represent a minority (about 20%) of NSCLC patients, RT plus IT may be a valuable option for many patients with BMs from NSCLC.

The present meta-analysis suggests that RT given before o concurrently with IT may provide better results than the inverse sequencing. This observation is consistent with the biological assumption for the synergism between IT and RT. In fact, RT given before IT may improve the BBB permeability thus allowing IT drugs to subsequently penetrate the BMs (van Vulpen et al., 2002). Furthermore, RT given before or concurrently with IT may enhance tumor antigen presentation, promote the local release of inflammatory cytokines and inhibit the functions of suppressor immune cells, thus contributing with IT to elicit the immune response (Demaria et al., 2005).

This meta-analysis has, however, some obvious limitations. Although our main outcome analysis on RT + IT treatment is biologically plausible and sound, the results of the included individual studies were dissimilar, as reflected in the significant heterogeneity. All studies were retrospective series with no prospective randomized studies so that only selected patients (younger? fit? Asymptomatic or oligosymptomatic?) may have received both RT followed/current to IT in the optimal sequence manner, with almost 50% that received RT after an ongoing systemic treatment. Even if 85% of studies regarded melanoma BMs, different participant characteristics in terms of DS-GPA group and biology (driver mutations) may have caused non-uniform results and led to potential heterogeneity. Finally, more than 50% of melanoma patients received ipilimumab monotherapy that is less effective that its combination with anti-PD-1 antibodies or anti-PD-1 antibodies alone. Although there was inevitable heterogeneity in the included studies, our systematic review still has some strengths: we included all published studies exploring activity of RT combined with IT for the treatment of BMs from melanoma and other solid tumors; we found that association of RT and IT provides a good OS with about 50% and 30% of patients alive at 1-year and 2-year respectively, and in particular we showed that the addition of IT to RT is significantly better than RT alone, with a 50% reduced risk of death and low-moderate toxicity.

Results from this meta-analysis can provide the basis for a rigorous exploration of the potential benefits of combining RT with novel systemic therapies such as IT, as recently advocated by the American Society for Radiation Oncology (ASTRO) in a specific guideline (Bristow et al., 2018). In this regard, there is currently growing research investigating the combination of RT and IT for the treatment of BMs. For example, an ongoing phase 3 trial is comparing fotemustine versus the combination of ipilimumab and fotemustine or the combination of ipilimumab and nivolumab in patients with metastatic melanoma with BMs (NCT02460068). A phase 1–2 study is also testing the combination of nivolumab + RT + ipilimumab for the control of intracranial disease in patients with NSCLC and BMs (NCT02696993).

Based on this systematic review and meta-analysis, the combination of IT and RT for the treatment of patients with BMs from melanoma and NSCLC has acceptable toxicity and prolongs OS, when compared with RT alone. RT given before or concurrently with IT seems to be the sequence with the best effect on outcome. RT modality, dose, fractioning and combinations with novel IT agents should be further investigated in specifically designed, prospective clinical trials.

Declaration of Competing Interest

The authors declare no conflict of interest.

Table 2
Characteristics of local and systemic treatments.

Author/year	RT type (%)	Dose median (Gy)	Timing RT (%)	IT drug (%)	N° cycles (median)	Main toxicities %
Acharya et al. (2017)	SRS (100)	20	0: before; 6: concurrent; 94: after	NIVO, PEMBRO or IPI: NR	4	Radionecrosis (1)
Ahmed et al. (2017)	SRS (82), SRT (18)	SRS: 20 SRT: 25	27: concurrent, 47: before, 26: after	NIVO:65, DURVALUMAB:35	–	–
An et al. (2017)	SRS (100)	20	100: after	IPI:100	–	–
Anderson et al. (2017)	WBRT (14); SRS (52); Post surgery (33)	WBRT: 30 SRS: 20	100: Concurrent	PEMBRO: 100	4	–
Chen et al. (2018)	SRS (100)	20	100:Concurrent	IPI, NIVO or PEMBRO: NR	–	Radionecrosis (3)
Choong et al. (2017)	WBRT (38.9) SRS (73.1)	–	100: Concurrent	IPI: 72; anti-PD-1: 28	–	Radionecrosis (2.8)
Diao et al. (2018)	SRS (100)	20	100: concurrent	IPI:100	4	Radionecrosis (2), hemorrhage (18)
Fang et al. (2017)	SRS or WBRT + SRS (100)*	20	39: before 61: after	IPI 87; PEMBRO 9; Both 4	–	Radionecrosis (27)
Gaudy-Marqueste et al. (2017)	SRS (100)	–	47: before 53: after	IPI 49; PEMBRO 40; both 11%	–	–
Gerber et al. (2015)	WBRT (100)	30	23: before 46: concurrent 31: after	IPI:100	4	G3-4 Cognitive changes (8)
Hubbeling et al. (2018)	WBRT (58) or PBI (16) or SRS (70)*	30 (WBRT); 30 (PBI); 18 (SRS)	60: before 40: concurrent	NIVO:78; PEMBRO:16; ATEZO: 8	9	Overall G3-4 (9) (SRS) & (10) (WBRT); Headache (4), anorexia (4), cognitive changes (4)
Kaidar-Person et al. (2017)	SRS (100)	21	55: before 7: concurrent 38: after	IPI 65.5 PEMBRO 24 NIVO 10.5	–	Radionecrosis (27.6); hemorrhage (24)
Kiess et al. (2015)	SRS (100)	21	41: SRS before IT 33: concurrent 26: SRS after IT	IPI: 100	4	Overall G3-4 (20); CNS bleeding (22), seizure (13), dermatitis (7)
Knisely et al. (2012)	SRS (100), WBRT (40.7)	–	41: SRS after IT 59: SRS before IT	IPI: 100	–	Radionecrosis (11)
Kotecha et al. (2017)	SRS (100)	–	100: before	PD-1 or IPI: 100	–	Radionecrosis (2)
Liniker et al. (2016)	WBRT (78) SRS (22)	30 (WBRT)**; ND (SRS)	WBRT: 19 sequential, 52 concurrent SRS: NR	PEMBRO: 77 NIVO: 20 Both: 3	–	G ≥ 3-4 (SRS): symptomatic radiation necrosis (17) G ≥ 3-4 (WBRT): cognitive changes (5), Stevens-johnson syndrome ^(5), nausea (5), rash (10)
Mathew et al. (2013)	SRS (100)	20	16: before; 28: concurrent; 40: after; 3: NR	IPI: 100	4	Intracranial hemorrhage (28), radionecrosis (0)
Nardin et al. (2018)	SRS (100)	20	38: concurrent; 36: before; 26: after	PEMBRO: 100	–	G3 radionecrosis (12)
Olson et al. (2016)	SRS (100)	20	54 before or concurrent; 46 after	IPI: 100	4	G3 CNS toxicities (11), radionecrosis (7)
Parakh et al. (2017)	SRS (23) WBRT(30) Chir + RT (46)	–	100: before	NIVO, PEMBRO: NR	–	–
Patel et al. (2017)	SRS (100)	20	60: after; 35: before; 5: concurrent	IPI: 100	–	Radionecrosis (30)
Pike et al. (2017)	WBRT (36) SRS (73) WBRT + SRS (36)	30 (WBRT) 20 (SRS)	78: before 59: before and after	PEMBRO, NIVO or IPI: NR	2	–
Qian et al. (2016)	SRS (100)	20	100: before	PEMBRO + NIVO: 28 IPI: 72	–	–
Qin et al. (2016)	SRT (100)	20 (ablative) 35 (non ablative)	–	IPI: 100	≥1	Dermatologic (27), gastrointestinal (18), fatigue (11), nausea (9), anorexia (5)
Rahman et al. (2018)	SRS (100)	18	100: concurrent	IPI: 68; PEMBRO:20; IPI + NIVO:6; NIVO:3; Other:3	–	Radionecrosis (14.3)
Schapira et al. (2018)	SRS (100)	18/1 fr (61%)	–	NIVO: 83.8	7	G3: ataxia (4.2), headache (4.2)

(*continued on next page*)

Table 2 (*continued*)

Author/year	RT type (%)	Dose median (Gy)	Timing RT (%)	IT drug (%)	N° cycles (median)	Main toxicities %
				PEMBRO: 5.4 ATEZO: 10.8		
Silk et al. (2013)	WBRT (48.5) SRS (51.5)		36: after 64: before	IPI: 100	–	–
Skrepnik et al. (2017)	SRS (100)	21		IPI: 100	4	–
Stokes et al. (2017)	SRS (50.3), WBRT (49.7)	–	–	Not specified	–	–
Tazi et al. (2015)	SRS (100)	–	100: before or concurrent	IPI: 100	4	Overall G3-4 (10); Diarrhoea (10)
Theurich et al. (2016)	WBRT (62); SRS (62)	30 (WBRT); 20 (SRS)	–	IPI: 89 (11 received RT in other sites + SNC RT)	4	Overall G3-4 (0)
Williams et al. (2017)	WBRT (31); SRS (69)	15-30 (WBRT); 30 (SRS)	31: concurrent; 69: before	IPI: 100	4 & 3°	Overall G3-4 (75); G3-4 diarrhoea (31)
Yusuf et al. (2016)	SRS (100); WBRT (5.6)	18	61: before; 39: concurrent/after	Anti-PD-1: 72 IPI:28	–	Radionecrosis (3.4)

*, Patients received a median of 2 treatments; °, for 3 and 10 mg/kg dose levels; *, patients received a median of 2 treatments; **, 6 patients received simultaneous integrated boost (45 Gy in 10 fractions) to larger lesions; ^concomitant phenytoin therapy; IPI, ipilimumab; PEMBRO, pembrolizumab; NIVO, nivolumab; WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery; RT, radiotherapy; Gy, gray; NR, not reported; G, grade.

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