European Journal of Cancer 112 (2019) 38–46

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Impact of radiotherapy administered simultaneously with systemic treatment in patients with melanoma brain metastases within MelBase, a French multicentric prospective cohort

Pauline Tétu [a,*], Clara Allayous [a,1], Bastien Oriano [b], Stéphane Dalle [c], Laurent Mortier [d], Marie-Thérèse Leccia [e], Bernard Guillot [f], Sophie Dalac [g], Caroline Dutriaux [h], Jean-Philippe Lacour [i], Philippe Saiag [j], Florence Brunet-Possenti [k], Julie De Quatrebarbes [l], Pierre-Emmanuel Stoebner [m], Delphine Legoupil [n], Marie Beylot-Barry [o], Thierry Lesimple [p], François Aubin [q], Brigitte Dreno [r], Sameh Mohamed [a], Alice Ballon [s], Raphaël Porcher [b,1], Céleste Lebbe [a,1]

[a] *APHP Dermatology, Department of Dermatology, Paris 7 Diderot University, INSERM U976, Hôpital Saint-Louis, Paris, France*
[b] *Clinical Epidemiology Center, AP-HP, Hôtel-Dieu, Paris, France*
[c] *Hospices Civils De Lyon, Pierre-Bénite, France*
[d] *Dermatology Department, CHRU Lille, Lille, France*
[e] *Dermatology Department, CHU Albert Michalon, Grenoble, University of Grenoble, Grenoble, France*
[f] *Dermatology Department, Universitary Hospital of Montpellier, CHU Montpellier, Montpellier, France*
[g] *Dermatology, University Hospital of Dijon, Dijon, France*
[h] *Dermatology and Pediatric Dermatology Department, Bordeaux Hospital, Bordeaux, France, Bordeaux, France*
[i] *Dermatology Department, Nice Hospital, Nice, France, Nice, France*
[j] *AP-HP, Dermatology, Ambroise Paré Hospital, Boulogne-Billancourt, France*
[k] *AP-HP, Dermatology, Bichat Hospital, Paris, France*
[l] *Dermatology, CHR Annecy Genevois, Annecy, France*
[m] *Dermatology, CHU de Nimes, Nimes, France*
[n] *Dermatology, CHU Brest, Brest, France*
[o] *Dermatology, Hôpital Saint-André, CHU de Bordeaux, Université de Bordeaux, Bordeaux, France*
[p] *Centre d'Oncodermatologie CLCC/CHU de Rennes, Rennes, France*
[q] *Dermatology, CHU de Besançon, Besançon, France*
[r] *Dermatology, CHU de Nantes, Nantes, France*
[s] *Data Management, AP-HP, Hôpital Saint-Louis, Paris, France*

Received 15 August 2018; received in revised form 27 January 2019; accepted 10 February 2019
Available online 22 March 2019

* *Corresponding author*: Dermatology; Saint-Louis Hospital, 1 avenue Claude Vellefaux, 75010 Paris, France. Fax: +33321338200.
E-mail address: pauline.tetu@hotmail.fr (P. Tétu).
[1] Co-authors have equally contributed to this study.

https://doi.org/10.1016/j.ejca.2019.02.009

KEYWORDS
Advanced melanoma;
Brain metastases;
Propensity score;
Radiotherapy;
Immunotherapy;
Targeted therapy

Abstract ***Background:*** Melanoma brain metastases (MBMs) are historically associated with poor prognosis. Radiation therapy is conventionally associated with a high local control rate. Development of targeted therapy and immunotherapy has improved overall survival (OS) and intracranial response rate, but about 50% of patients failed to respond to these novel therapies. The objective of this study was to assess the impact of combined radiotherapy (cRT) on overall survival in a large multicenter real-life prospective cohort of patients with MBM treated with immunotherapy or targeted therapy.

Patients and methods: Clinical data from 262 patients with MBM were collected via MelBase, a French multicentric biobank prospectively enrolling unresectable stage III or IV melanoma. Two groups were defined: patients receiving cRT (cRT group) or not receiving cRT (no-cRT group). Primary end-point was OS. Propensity score weighting was used to correct for indication bias.

Results: Among the 262 patients, 93 (35%) received cRT (cRT group). The patients were treated with immunotherapy in 69% and 60% and with targeted therapy in 31% and 40% of the cRT and no-cRT groups, respectively. With a median follow-up of 6.9 months, median OS was 16.8 months and 6.9 months in the cRT and no-cRT groups, respectively. After propensity score weighting, cRT was associated with longer OS (hazard ratio = 0.6, 95% confidence interval: 0.4–0.8; p=0.007). Median OS after ponderation was 15.3 months and 6.2 months in the cRT and no-cRT groups, respectively.

Conclusion: This study shows that cRT may be associated with a significant decrease of 40% in the risk of death in patients with MBM treated with systemic therapy.

1. Introduction

Although melanoma brain metastases (MBMs) are associated with a poor prognosis with a historical median overall survival (OS) of approximately 4 months [1–4], development of new systemic therapies and advances in radiation therapy (RT) has improved clinical outcomes.

Stereotactic radiosurgery (SRS) alone achieves a high local control rate of up to 90% [5–8], but distant disease control remains poor and benefit in OS is limited with a median survival of about 4 months [2,7,8].

The development of targeted therapy and immunotherapy has significantly improved the prognosis of metastatic melanoma including MBM with a median OS for patients with MBM of about 7 months for ipilimumab [9], 10 months for pembrolizumab and nivolumab [10,11] and up to 24 months for BRAF and MEK inhibitors [12]. Recently, combination therapy with anti-PD1 and anti-CTLA4 showed unprecedented results with up to 57% of intracranial objective response rate (ORR) [13,14]. Despite these encouraging data, about 50% of patients failed to respond to these novel therapeutics and response duration is shorter than that in extracranial disease, hence emphasising the need of additional combination strategy and identification of predictive or prognostic biomarkers.

Recent non-randomised clinical studies suggest that RT in combination with anti-BRAF ± anti-MEK as well as with anti-CTLA4 or anti-PD1 antibodies could be synergistic, without increasing toxicities in MBM treatment [15–20]. Interestingly, timing seemed to have a major impact on this synergic effect with better clinical outcomes for combined treatment [15,21–23]. However, these studies present an important bias as combined treatment or RT alone is neither randomly allocated nor given in a standardised schedule.

One way to overcome this conceptual shortcoming in the design of observational studies is the use of propensity scores to adjust for differences of patient's characteristics between two groups and to limit confusion and selection bias [24].

In this study, we evaluated the impact of combined RT (cRT) on OS in a large multicenter real-life prospective cohort of patients with MBM treated with immunotherapy or targeted therapy, using propensity score.

2. Materials and methods

2.1. Patient population

Patients included in this study were identified via MelBase, a French clinical database with a biobank dedicated to the prospective follow-up of adult patients with advanced melanoma. This observational cohort included standardised questionnaires completed prospectively by the investigator at inclusion and throughout disease's course. All participating centres were oncodermatology or oncology units contributing to clinical studies with high experience in management of patients with MBM and included all incident cases as a rule. MelBase protocol was approved by the French

ethics committee (CPP Ile-de-france XI, n°12027, 2012) and registered in the NIH clinical trials database (NCT02828202). Written informed consent was obtained from all patients.

All patients within MelBase presenting at least one MBM, with at least one postbaseline tumour assessment and treated with systemic therapies at MBM diagnosis between December 2013 and December 2017 were included. Patient and treatment characteristics were collected retrospectively. The indication of RT was based on investigator's choice after discussion in tumour boards in accordance with European recommendations and evidence-based medicine.

Patients were divided into two groups:

- cRT group: patients treated with cRT;
- No-cRT group: patients treated with non-cRT or not treated with radiotherapy.

RT was considered combined if delivered from 30 days before the first systemic therapy dose to treat MBM until 30 days after the first dose of the same therapy line. All lesions treated with RT within a timing of more than 30 days from the start of the same therapy line were included in the no-cRT group. cRT was performed as per local practices and included whole brain radiotherapy (WBRT) alone, SRS alone or WBRT after SRS.

Patients were treated by either targeted therapy (anti-BRAF ± anti-MEK) or immunotherapy (ipilimumab or anti-PD1), according to investigator's choice.

2.2. End-points

In both groups, date of the first systemic treatment administration for MBM is considered as the baseline.

The primary end-point was OS, defined as the time from the baseline to death from any cause or the end of follow-up. The secondary end-points were progression-free survival (PFS), ORR and safety. PFS is defined as time from the baseline to clinical or radiological progression or death from any cause. 'Clinical or radiological progression' was defined by the presence of new lesions or progression of existing lesions on clinical and radiological evaluation during the prospective follow-up according to RECIST 1.1, based on local investigator interpretation [25]. Radiological evaluation included brain magnetic resonance imaging, and total body imaging (positron-emission tomography scan or computed tomography scan) was performed every three months. ORR was defined as the proportion of patients with complete response (CR) or partial response (PR) as best overall response. Adverse events (AEs) were assessed according to the Common Terminology Criteria for Adverse Events (version 4.0).

2.3. Statistical analysis

Propensity score weighting was used to estimate the benefit of radiotherapy [26,27]. The propensity score is the probability of receiving treatment for a patient with specific covariates. Inverse probability of treatment weighting (IPTW) consists in weighting each observation by the inverse of the estimated probability of having received the treatment actually given conditional on covariates.

IPTW weights were obtained by using logistic regression for radiotherapy. The following variables collected at the time of the first systemic treatment administration were considered in this propensity score model: sex, age, treatment line, BRAF mutation status, Eastern Cooperative Oncology Group (ECOG) status, lactate dehydrogenase (LDH) level, liver metastases, symptomatic brain metastases, corticosteroids, number of metastases organ sites and number of MBMs. MBMs were considered as symptomatic in patients who had neurological symptoms related to brain metastases or leptomeningeal disease or any combination of these. The factor 'corticosteroids' included all patients receiving corticosteroids to control neurological symptoms related to brain metastases, regardless of the doses and the regimen used. We used truncated weights, and we trim high weights at the 90th percentile. To check that the propensity score model was successful in balancing groups, imbalance in patient characteristics between groups before and after weighting was measured by standardised differences. We considered standardised differences above 10% as representing meaningful imbalance.

Analysis was based on using a Cox regression model in the weighted sample to compare the hazard of death between the cRT and no-cRT groups, with a robust variance estimator. Weighted overall survival curves were also estimated [28].

Missing data were handled by using multiple imputation by chained equations. Twenty imputed data sets were imputed and analysed separately, and results were then pooled into a final estimate.

We additionally performed several sensitivity analyses to the IPTW analysis method. We first used covariate adjustment in a Cox model. To avoid a bias due to a missing covariate that can be a confounding factor, we used toxicity of grade III/IV like covariate in a Cox regression model.

Then, we also used full matching on the logit of the propensity score, which has been shown to be a valid alternative to the more common IPTW approach [29]. In the PS matching, the implementation is pair matching: pairs of treated and control individuals are formed and they shared a similar value of the propensity score.

We matched individuals on the logit of the propensity score using a calliper width that was defined as a

proportion of the standard deviation of the logit of the propensity score.

In fine, we used weights generated by full matching approach in a Cox regression model to compare the hazard of death between the cRT and no-cRT groups, with a robust variance estimator.

To assess the potential effect of unmeasured confounding on the results, we computed the E-value [30]. The E-value is defined as the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away a specific treatment-outcome association, conditional on the measured covariates. A small E-value means that a small amount of confounding would be sufficient to explain away an effect estimate. The lowest possible value is 1. Conversely, a higher E-value means that considerable unmeasured confounding would be needed to explain away the observed effect.

All analyses were carried out using R statistical software, version 3.3.1 (the R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient characteristics

A total of 262 patients were identified between December 2013 and December 2017. Among them, 93 (35%) received cRT (cRT group) (Fig. 1). Patient characteristics are summarised in Table 1. In the whole population, median age was 61 years (Q1-Q3: 50–69) and 57% of patients were male. DS-GPA (disease-specific Graded Prognostic Assessment) was not significantly different between the two groups (p = 0.98). In the cRT group, 81 patients received SRS (87%), 12 patients received WBRT (13%) and 21% received non-combined RT in addition to combined RT. Twenty-five patients (25%) of the no-cRT group received non-combined RT for MBM (64% SRS and 36% WBRT) with a median time interval of 60 days from the start of the end of the systemic therapy. At the baseline, 69% and 60% of patients were treated with immunotherapy and 31% and 40% with targeted therapy in the cRT group and no-cRT group, respectively.

3.2. Comparability of the groups and development of the propensity score

Before propensity score analysis, baseline patient characteristics were not significantly different for the following variables: sex (imbalance = −1%), ECOG status (imbalance = 9%), LDH level (imbalance = −2%), line of systemic treatment (imbalance = −9%), BRAF status (imbalance = −3%), neurological symptoms (imbalance = −1%), systemic treatment (imbalance = −7%), corticosteroid treatment (imbalance = 9%) and number of MBM (imbalance = -4%) (Table 2). Using a Cox regression model, we obtained significantly hazard ratio (HR) (stratified on RT) for the following variables: sex (HR = 0.83; 95% confidence interval [CI]: 0.75–0.88), ECOG status (HR = 2.4; 95% CI: 2.1–2.8) LDH level (HR = 2.1; 95% CI: 1.9–2.2), line of systemic treatment (HR = 1.7; 95% CI: 1.3–2.3), number of metastatic sites (HR = 1.3; 95% CI: 1.1–1.5), combined hepatic metastases (HR = 1.8; 95% CI: 1.4–2.1), corticosteroid treatment (HR = 1.4; 95% CI: 1.1–1.7) and number of MBMs (HR = 1.13; 95% CI: 1.13–1.16) (Table 2). After propensity score weighting,

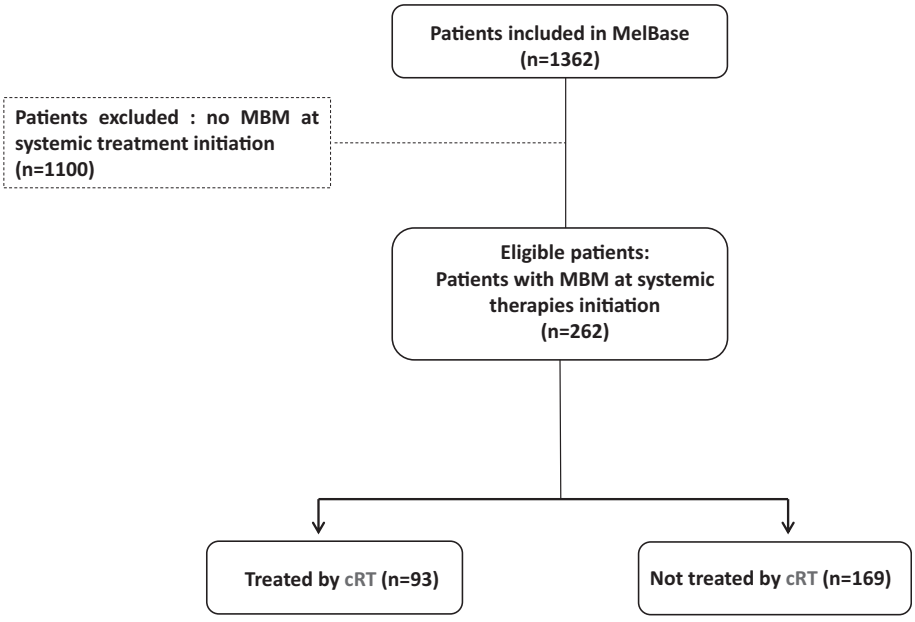

Fig. 1. Trial profile. MBM: melanoma brain metastases; cRT: combined radiotherapy; no-cRT: no combined radiotherapy.

Table 1
Patient and disease characteristics.

Patient and disease characteristics	All patients, N = 262	cRT group, N = 93	No-cRT group, N = 169
Age (years, range)			
Mean	61 (50–69)	58 (50–67)	63 (50–71)
<65 (N; %)	163 (62)	67 (72)	96 (57)
≥65 (N; %)	99 (38)	26 (28)	73 (43)
Sex			
Male (N; %)	151 (57)	53 (57)	98 (58)
Female (N; %)	111 (42)	40 (43)	71 (42)
Performance status (N; %)			
0–1	232 (89)	88 (94)	144 (85)
2–3	27 (10)	5 (5)	22 (13)
4	1 (1)	–	1 (1)
Not available	2 (1)	–	2 (1)
LDH (N; %)			
< ULN	155 (59)	52 (56)	103 (61)
≥ ULN	101 (39)	39 (42)	62 (37)
≥2 ULN	27 (10)	9 (10)	18 (11)
Not available	6 (2)	2 (2)	4 (2)
BRAF mutation status (N; %)			
Wild-type	108 (41)	35 (38)	73 (43)
Mutated	154 (59)	58 (62)	96 (57)
Number of metastatic sites (N; %)			
<3	80 (31)	27 (29)	53 (31)
≥3	182 (69)	66 (71)	116 (69)
Liver metastasis (N; %)	80 (31)	28 (30)	52 (31)
Number of % MBM (N; %)			
<3	120 (44)	40 (43)	80 (47)
≥3	103 (39)	39 (42)	64 (38)
Not available	39 (15)	14 (15)	25 (15)
Solitary MBM	29 (11)	8 (9)	21 (12)
Leptomeningeal involvement (N; %)	25 (10)	13 (14)	12 (7)
Neurological symptom (N; %)	107 (41)	39 (42)	68 (40)
Use of corticosteroids (N; %)	107 (41)	39 (42)	68 (40)
DS-GPA (N; %)			
0	**101 (39)**	**35 (38)**	**66 (39)**
1	**84 (32)**	**30 (32)**	**54 (32)**
2	**77 (29)**	**28 (30°)**	**49 (29)**
Type of concomitant RT (N; %)			
WBRT	–	12 (13)	–
SRS	–	81 (87)	–
Use of non-concomitant RT (N; %)			
WBRT	–	5 (5%)	9 (5%)
SRS	–	15 (16%)	16 (9%)
Line of systemic therapy (N; %)			
First line	160 (61)	51 (55)	109 (65)
Second line or more	102 (39)	42 (45)	60 (36)
Systemic therapy (N; %)			
Anti-PD1	118 (45)	52 (56)	66 (39)
Anti-CTLA4	48 (18)	12 (13)	36 (21)
BRAFi alone	43 (16)	11 (12)	32 (19)
BRAFi + MEKi	53 (20)	18 (19)	35 (21)

LDH: lactate dehydrogenase; ULN: upper limit of normal; MBM: melanoma brain metastases; WBRT: whole brain radiotherapy; SRS: stereotactic radiosurgery; BRAFi: BRAF inhibitor; MEKi: MEK inhibitor.
The bold values are the number of patients and the percentage of patients (in brackets) with a DS-GPA (Diagnosis specific Graded Prognostic Assessment) equal to 0, 1 or 2.

the groups were comparable for all these factors (Table 2).

3.3. OS, PFS and ORR

At the time of analysis, 51% of patients in the cRT group and 62% in the no-cRT group were dead from disease progression. With a median follow-up of 6.9 months (range: 0.2–58.4), median OS was 16.8 months (95% CI: 11.8–27.9) in the cRT group and 6.9 months (95% CI: 5.4–9.4) in the no-cRT group (Fig. 2). Median OS after ponderation was 15.3 months and 6.2 months in the cRT and no-cRT groups, respectively. Estimated 1-year and 2-year OS were, respectively, 58.9% (95% CI:

Table 2
Imbalance before and after IPTW (inverse probability of treatment weighting) for patient and disease characteristics included in the propensity score.

Variables	Before propensity score		After propensity score
	Imbalance (%)	HR (CI)	Imbalance (%)
Sex	−1	0.83 (0.75–0.88)	2
Age	−18	1.12 (0.95–1.52)	−1
ECOG	9	2.44 (2.12–2.77)	1
LDH: < ULN versus ≥ ULN	−2	2.08 (1.92–2.21)	0
Neurological symptoms	−1	1.27 (0.99–1.65)	0
Corticosteroids	9	1.42 (1.09–1.70)	3
Number of metastatic sites	11	1.32 (1.09–1.45)	10
Number of MBM	**−4**	**1.13 (1.11–1.16)**	**1**
Hepatic metastases	10	1.76 (1.40–2.11)	−1
BRAF status	−3	0.81 (0.76–1.03)	1
Line of treatment	−9	1.71 (1.25–2.33)	2
Systemic treatment	−7	1.12 (0.85–1.36)	−9

ECOG: Eastern Cooperative Oncology Group; CI: confidence interval; HR: hazard ratio; LDH: lactate dehydrogenase; ULN: upper limit of normal; MBM: melanoma brain metastases.
The bold values is the result (in percentage) of the imbalance before and after propensity score for the variables "number of MBM".

49.2–70.5) and 37.4% (95% CI: 27.6–50.7) for the cRT group and 33.8% (95% CI: 27–42.5) and 22.4% (95% CI: 16.1–31.3) for the no-cRT group. cRT was associated with higher OS in patients with MBM treated either with immunotherapy or targeted therapy compared with those who did not received cRT (HR = 0.60, 95% CI: 0.4 to 0.8; p=0.007) (Fig. 2). Sensitivity analyses confirmed this result as the HR was significant when toxicity was used as an adjustment variable (HR = 0.70; 95% CI: 0.64–0.79) and when full matching method was applied (HR = 0.61, 95% CI: 0.58–0.63). The E-value for the observed association between radiotherapy and mortality after adjustment for measured confounders was 3.7. This means that an unmeasured confounder should be associated with a risk ratio of 3.7-fold for both the likelihood of death and radiotherapy to explain away the obtained effect of cRT but weaker confounding could not do so. Results, therefore, seem robust because only very strong unmeasured confounding would challenge the association observed between radiotherapy and mortality.

Median PFS was 5.2 months (95% CI: 3.5–7.9) in the cRT group and 3.5 (95% CI: 2.7–4.5) in the no-cRT group, with no statistical difference (p=0.23). The 6-month and 18-month PFS was 44.4% (95% CI: 35.1–56.2) and 23.1% (95% CI: 15.5–34.4) in the cRT group and 31.2% (95% CI: 24.8–39.4) and 17.1% (95% CI: 11.8–24.7) in the no-cRT group, respectively (Fig. 3).

ORR and disease control rate were similar between the two groups (37% and 59% in the cRT-group versus 31% and 60% in the no-cRT group, respectively; p = 0.8) (Table 3).

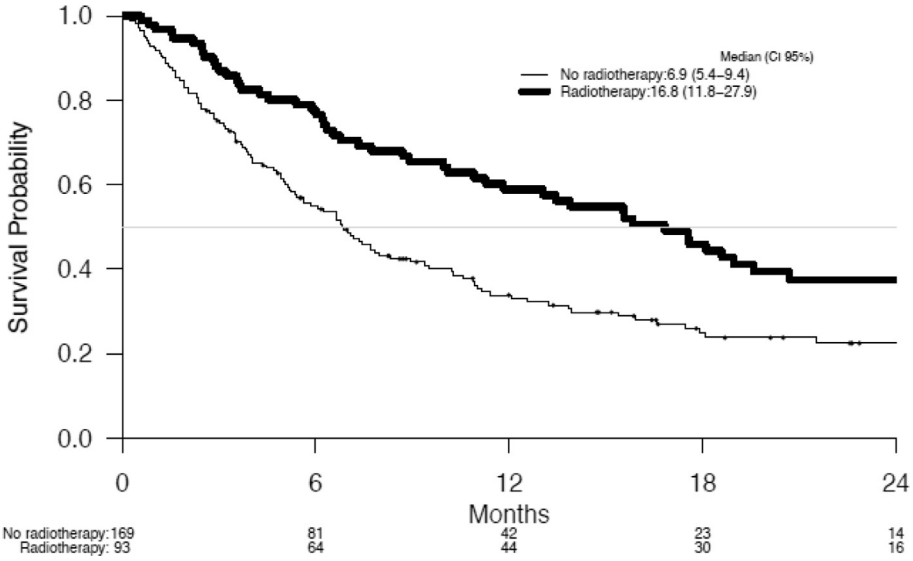

Fig. 2. Overall survival of patients treated with combined radiotherapy (cRT group) and patients not treated with combined radiotherapy (no-cRT group). cRT: combined radiotherapy; no-cRT: no combined radiotherapy.

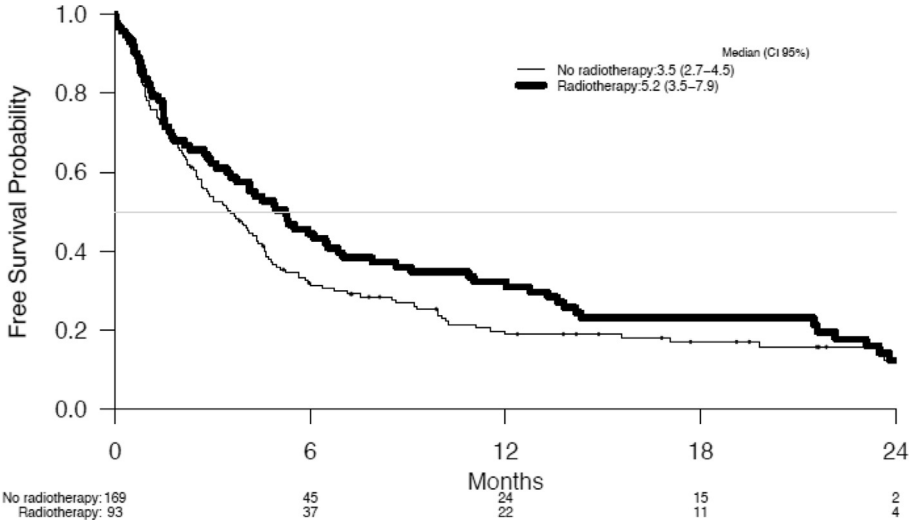

Fig. 3. Progression-free survival of patients treated with combined radiotherapy (cRT group) and patients not treated with combined radiotherapy (no-cRT group). cRT: combined radiotherapy; no-cRT: no combined radiotherapy.

3.4. Clinical outcomes according to the type of systemic treatment

In the cRT group (n = 93), median OS was 16.8 months (range: 11.8, not reached) for immunotherapy and 15.6 months (range: 10.9, not reached) for targeted therapy. The estimated 18-month OS was 43.3% (95% CI: 32.4–60.1) with immunotherapy and 45.7% (95% CI: 29.8–70) with targeted therapy. Estimated 18-month PFS was 21.4 (95% CI: 13.3–42.6) with immunotherapy and 24.1 (95% CI: 15.4–44.4) with targeted therapy. ORRs were 33% with immunotherapy and 45% with targeted therapy.

3.5. Tolerance

The incidence of AEs of any grade was 73% in the cRT-group and 61% in the no-cRT group (p = 0.4) (Supplementary Data S1). Grade III–IV AEs were reported in 20% in the RT group and 23% in the non-RT group.

Table 3
Best overall response rate.

Best overall response rate	RT group (n = 93)	No-RT group (n = 169)	p-value
Best response, N (%)			
CR	12 (13)	10 (6)	–
PR	22 (24)	43 (25)	–
SD	21 (23)	48 (28)	–
PD	38 (41)	68 (40)	–
ORR	34 (37)	53 (31)	p = 0.8
DCR	55 (59)	101 (60)	p = 0.8

RT: radiation therapy; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: objective response rate (CR + PR); DCR: disease control rate (CR + PR + SD).

4. Discussion

In patients with MBM treated with immunotherapy or targeted therapy, cRT is associated with an increased OS. The risk of death was decreased by 40% for patients treated with cRT, in comparison with those who did not receive cRT (p = 0.007).

This large real-life cohort of patients with MBM is of importance regarding clinical practice because these patients are usually excluded from clinical trials, and data are needed to improve their management. The major survival benefit observed in this study suggests that all eligible patients with MBM should be treated with cRT, regardless of systemic treatment received.

To date, only three retrospective studies have assessed the survival of patients with MBM treated with cRT and new systemic therapies [16–18]. In a cohort of 96 patients with MBM treated with SRS within 3 months of receiving systemic therapy, Ahmed *et al.* reported that anti-PD1, anti-CTLA4 and BRAF ± MEK inhibitors significantly improved OS when compared with chemotherapy. Indeed, 12-month OS was 48% for anti-PD1, 41% for anti-CTLA4 and 65% for BRAF and MEK inhibitors, compared with 10% with chemotherapy [18]. In a second cohort of 79 patients with MBM receiving systemic therapy within 6 weeks of SRS, median OS was 7.5 months for anti-CTLA4, 20.4 months for anti-PD1 and 17.8 months for BRAF ± MEK inhibitors and was significantly superior to median OS observed for those who did not receive any systemic drug therapy (10.8 months) [16]. In a recent retrospective study of 179 patients with MBM treated with Gamma Knife at the first MBM and retreated in case of new MBM, Gaudy-Marqueste *et al.* [17] reported that anti-PD1 or anti-CTLA4 and BRAF ± MEK inhibitors were significantly and highly

protective with a median OS of 10.95 months for patients receiving systemic therapy versus 2.29 months in those who did not receive immunotherapy or targeted therapy. However, survival analyses in these studies were not stratified on several potentially important confounding factors, leading to significant interpretation bias and difficult interpretation of results.

In previous studies, combined RT with immunotherapy or targeted therapy was always compared with RT alone or with RT and chemotherapy. To the best of our knowledge, this study is the first assessing the impact on survival of cRT in patients with MBM treated with systemic therapy. Although no direct comparisons were possible, our results are in accordance with those published data [16–18].

The observational design of this real-life study lead to confusion bias that we have taken into account with propensity score, a powerful statistical system representing an alternative to a randomised-controlled trial [24]. This statistical analysis enables to take into account confusion bias using a score that synthesises the influence on treatment choice of clinical parameters evaluated before. It permits in a non-randomised context to limit bias by adjusting on potential confusion factors [24].

We showed that cRT had a statistically significant protective effect in terms of survival, after adjusting for the main confounding factors identified in the literature [1,3,4]. In a retrospective cohort of 101 patients treated with ipilimumab for advanced melanoma, Koller *et al.* [31] recently reported a similar protective effect of concurrent RT with a median OS which more than doubled in patients receiving concurrent radiotherapy (external beam radiation or SRS) during or within 2 weeks of ipilimumab compared with those treated with ipilimumab alone (19 months versus 10 months, respectively). However, this study included only 8% of patients with MBM, and most patients received extracranial radiotherapy.

There is some evidence of the synergistic effect of RT and systemic therapy in the literature. Indeed, RT can cause a transient disruption in the blood–brain barrier [32], resulting in an uptake of systemic therapy. Moreover, the combination of RT and immunotherapy may increase systemic antitumour response by facilitating antigen presentation and T-cell activation [33,34]. Some clinical studies reported that combining RT and immunotherapy could lead to an abscopal effect, correlating with prolonged survival [35,36].

Although the retrospective design did not allow to assess specific neurologic toxicity, no increasing rate of toxicities was observed in the RT group. This result is in accordance with the acceptable toxicity profile of combined RT and systemic therapy described in the literature [15,19,37,38].

The main limitations of this study are the absence of central review of neuroimaging and the real-life design of MelBase where radiotherapy indications are left to investigator's decision. The non-randomised design of this study induces bias which is minimised with propensity score and sensitivity analyzes. However, the strength of results is inferior to prospective randomised studies. In fact, although the statistical model takes into account the most important known prognostic factors of patients with MBM, some other variables may persist. Moreover, missing data may limit the strength of results and lead to some unavailable information such as intracranial versus extracranial response. Although clinical trial may be the best way to assess the impact of cRT in patients with MBM, it raises specific ethical issues of randomising radiotherapy.

5. Conclusion

In this study, cRT was associated with a significantly higher OS in patients treated with systemic therapy. Further prospective studies are needed to determine the optimal timing to maximise the synergic effect and to better define the safety profile of cRT and systemic therapy.

Acknowledgement

The authors would like to thank Mathieu Momenzadeh, Emmanuelle Liegey, DRCI-AP and all clinical research assistants for their contributions to this study.

Funding/support

None but MelBase is sponsored by the French National Cancer Institute (INCa), BMS, MSD, Novartis and Roche.

Conflict of interest statement

A.C. reports personal fees from Roche, Amgen and BMS outside the submitted work. M.L. reports personal fees and others from Roche, BMS and Novartis outside the submitted work. D.C. reports personal fees and others from Amgen, Novartis, Roche, BMS, MSD and Merck Serono outside the submitted work. S.P. reports personal fees from Novartis, BMS and MSD outside the submitted work. L.T. reports personal fees from Roche, MSD, Novartis and Incyte outside the submitted work. L.C. reports grants and personal fees from Roche and BMS and personal fees from Novartis, MSD, Amgen, Pierre Fabre, Pfizer and Incyte outside the submitted work. All other authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.02.009.

References

[1] Davies MA, Liu P, McIntyre S, et al. Prognostic factors for survival in melanoma patients with brain metastases. Cancer 2011;117:1687–96.

[2] Fife KM, Colman MH, Stevens GN, et al. Determinants of outcome in melanoma patients with cerebral metastases. J Clin Oncol 2004;22:1293–300.

[3] Bedikian AY, Wei C, Detry M, et al. Predictive factors for the development of brain metastasis in advanced unresectable metastatic melanoma. Am J Clin Oncol 2011;34:603–10.

[4] Gumusay O, Coskun U, Akman T, et al. Predictive factors for the development of brain metastases in patients with malignant melanoma: a study by the Anatolian society of medical oncology. J Cancer Res Clin Oncol 2014;140:151–7.

[5] Yu C, Chen JCT, Apuzzo MLJ, et al. Metastatic melanoma to the brain: prognostic factors after gamma knife radiosurgery. Int J Radiat Oncol Biol Phys 2002;52:1277–87.

[6] Ramakrishna N, Margolin KA. Multidisciplinary approach to brain metastasis from melanoma; local therapies for central nervous system metastases. Am Soc Clin Oncol Educ Book 2013;399.403.

[7] Liew DN, Kano H, Kondziolka D, et al. Outcome predictors of Gamma Knife surgery for melanoma brain metastases. Clinical article. J Neurosurg 2011;114:769–79.

[8] Neal MT, Chan MD, Lucas JT, et al. Predictors of survival, neurologic death, local failure, and distant failure after gamma knife radiosurgery for melanoma brain metastases. World Neurosurgvol. 82; 2014. p. 1250–5.

[9] Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol 2012;13:459–65.

[10] Parakh S, Park JJ, Mendis S, et al. Efficacy of anti-PD-1 therapy in patients with melanoma brain metastases. Br J Canc 2017;116:1558–63.

[11] Goldberg SB, Gettinger SN, Mahajan A, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. Lancet Oncol 2016;17:976–83.

[12] Davies MA, Saiag P, Robert C, et al. Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. Lancet Oncol 2017;18:863–73.

[13] Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol 2018;19:672–81.

[14] Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. N Engl J Med 2018;379:722–30.

[15] Kiess AP, Wolchok JD, Barker CA, et al. Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: safety profile and efficacy of combined treatment. Int J Radiat Oncol Biol Phys 2015;92:368–75.

[16] Choong ES, Lo S, Drummond M, et al. Survival of patients with melanoma brain metastasis treated with stereotactic radiosurgery and active systemic drug therapies. Eur J Cancer 2017;75:169–78.

[17] Gaudy-Marqueste C, Dussouil AS, Carron R, et al. Survival of melanoma patients treated with targeted therapy and immunotherapy after systematic upfront control of brain metastases by radiosurgery. Eur J Cancer 2017;84:44–54.

[18] Ahmed KA, Abuodeh YA, Echevarria MI, et al. Clinical outcomes of melanoma brain metastases treated with stereotactic radiosurgery and anti-PD-1 therapy, anti-CTLA-4 therapy, BRAF/MEK inhibitors, BRAF inhibitor, or conventional chemotherapy. Ann Oncol 2016;27:2288–94.

[19] Liniker E, Menzies AM, Kong BY, et al. Activity and safety of radiotherapy with anti-PD-1 drug therapy in patients with metastatic melanoma. OncoImmunology 2016;5:e1214788.

[20] Gaudy-Marqueste C, Carron R, Delsanti C, et al. On demand Gamma-Knife strategy can be safely combined with BRAF inhibitors for the treatment of melanoma brain metastases. Ann Oncol 2014;25:2086–91.

[21] Schoenfeld JD, Mahadevan A, Floyd SR, et al. Ipilmumab and cranial radiation in metastatic melanoma patients: a case series and review. J Immunother Cancer 2015;3:50.

[22] Silk AW, Bassetti MF, West BT, et al. Ipilimumab and radiation therapy for melanoma brain metastases. Cancer Med 2013;2:899–906.

[23] An Y, Jiang W, Kim BYS, et al. Stereotactic radiosurgery of early melanoma brain metastases after initiation of anti-CTLA-4 treatment is associated with improved intracranial control. Radiother Oncol 2017;125:80–8.

[24] Dugoff EH, Schuler M, Stuart EA. Generalizing observational study results: applying propensity score methods to complex surveys. Health Serv Res 2014;49:284–303.

[25] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

[26] Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11:550–60.

[27] Lunceford JK, Davidian M. Stratification and weighting via the propensity score in estimation of causal treatment effects: a comparative study. Stat Med 2004;23:2937–60.

[28] Cole SR, Hernán MA. Adjusted survival curves with inverse probability weights. Comput Methods Progr Biomed 2004;75:45–9.

[29] Austin PC, Stuart EA. The performance of inverse probability of treatment weighting and full matching on the propensity score in the presence of model misspecification when estimating the effect of treatment on survival outcomes. Stat Methods Med Res 2017;26:1654–70.

[30] VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med 2017;167:268–74.

[31] Koller KM, Mackley HB, Liu J, et al. Improved survival and complete response rates in patients with advanced melanoma treated with concurrent ipilimumab and radiotherapy versus ipilimumab alone. Cancer Biol Ther 2017;18:36–42.

[32] Cao Y, Tsien CI, Shen Z, et al. Use of magnetic resonance imaging to assess blood-brain/blood-glioma barrier opening during conformal radiotherapy. J Clin Oncol 2005;23:4127–36.

[33] Twyman-Saint Victor C, Rech AJ, Maity A, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature 2015;520:373–7.

[34] Reits EA, Hodge JW, Herberts CA, et al. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. J Exp Medvol. 203;2006. p. 1259–71.

[35] Grimaldi AM, Simeone E, Giannarelli D, et al. Abscopal effects of radiotherapy on advanced melanoma patients who progressed after ipilimumab immunotherapy. OncoImmunology 2014;3:e28780.

[36] Chandra RA, Wilhite TJ, Balboni TA, et al. A systematic evaluation of abscopal responses following radiotherapy in patients with metastatic melanoma treated with ipilimumab. OncoImmunology 2015;4:e1046028.

[37] Ahmed KA, Freilich JM, Sloot S, et al. LINAC-based stereotactic radiosurgery to the brain with concurrent vemurafenib for melanoma metastases. J Neuro Oncol 2015;122:121–6.

[38] Nardin C, Mateus C, Texier M, et al. Tolerance and outcomes of stereotactic radiosurgery combined with anti-programmed cell death-1 (pembrolizumab) for melanoma brain metastases. Melanoma Res 2018;28:111–9.