Original Article

Melanoma brain metastases: the outcome of whole brain radiation therapy in the era of effective systemic therapy

Cora Waldstein[1,2], Wei Wang[1,3,4], Serigne Lo[3], Brindha Shivalingam[3,5], Gerald B. Fogarty[3,6], Matteo S. Carlino[3,4,7], Alexander M. Menzies[3,4,8], Georgina V. Long[3,4,8], Angela M. Hong[3,4,6]

[1]Department of Radiation Oncology, Westmead Hospital, Westmead, New South Wales, Australia; [2]Department of Radiation Oncology, Comprehensive Cancer Center, General Hospital of Vienna, Medical University of Vienna, Währinger Gürtel, Austria; [3]Melanoma Institute Australia, The University of Sydney, Sydney, New South Wales, Australia; [4]Sydney Medical School, The University of Sydney, Sydney, New South Wales, Australia; [5]Department of Neurosurgery, Royal Prince Alfred Hospital, New South Wales, Australia; [6]Genesiscare, Radiation Oncology, Mater Hospital, New South Wales, Australia; [7]Department of Medical Oncology, Crown Princess Mary Cancer Centre, Westmead Hospital, New South Wales, Australia; [8]Department of Medical Oncology, Royal North Shore Hospital, New South Wales, Australia

Contributions: (I) Conception and design: AM Hong, C Waldstein, W Wang; (II) Administrative support: None; (III) Provision of study materials or patients: AM Hong, W Wang, GB Fogarty, GV Long, MS Carlino, AM Menzies, B Shivalingam; (IV) Collection and assembly of data: AM Hong, C Waldstein; (V) Data analysis and interpretation: AM Hong, C Waldstein, S Lo, GB Fogarty; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Prof. Angela M. Hong. Melanoma Institute Australia, The University of Sydney, 40 Rocklands Road, North Sydney NSW 2060, Australia. Email: angela.hong@sydney.edu.au.

Background: Whole brain radiation therapy (WBRT) is sometimes recommended for patients with multiple melanoma brain metastases (MBM) in addition to systemic therapy and/or local therapy. We report outcomes of WBRT and identify associated factors in the era of modern systemic therapy.

Methods: Ninety patients treated with WBRT between 2011 and 2018 were included. Records were analyzed for clinical and treatment characteristics, radiation techniques, systemic therapy and outcomes. Overall survival (OS) rates were calculated using the Kaplan-Meier method; factors affecting OS were assessed using the log-rank test as well as Cox regression.

Results: The median age was 63 years and the median follow-up was 4.5 months. The median OS from diagnosis of MBM was 8 months (range, 1–83 months), median OS from the beginning of WBRT was 5 months (range, 0–64 months). Patients with BRAF mutation who had prior systemic treatment (n=31) had a median OS from WBRT of 4.6 versus 5.2 months for those with BRAF wild type disease (n=27). Patients with no systemic treatment prior to WBRT (n=32) had a median survival of 6.7 months (P=0.65). In multivariable analysis, the presence of neurological symptoms was associated with worse OS (P=0.029) and prior surgery with better OS (P=0.002).

Conclusions: In selected patients with MBM treated with systemic therapy with known intracranial activity, WBRT is a treatment option in selected patients after local therapy (surgery and SRS). Future studies should further determine the role of systemic treatment in combination with radiotherapy (RT) in MBM patients, particularly in patients with multiple brain metastases.

Keywords: Melanoma; brain metastasis; radiotherapy (RT); immunotherapy; targeted therapy

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Introduction

Melanoma has a high propensity to metastasise into the brain in patients with advanced disease (1). Brain metastases are associated with poor prognosis and often result in deterioration in neurological function and quality of life and/or neurological death (2-4). The treatment approach to melanoma brain metastases (MBM) is multimodal including systemic therapy, often in combination with brain directed local therapy such as surgical resection and radiotherapy (RT).

The use of whole brain radiation therapy (WBRT) is declining due to the intracranial activity of systemic drug therapies in melanoma (targeted therapy and immunotherapy (5-7), increasing evidence for use of stereotactic radiosurgery (SRS) in multiple brain metastases (8), the lack of efficacy in the adjuvant setting (9), and the toxicity of WBRT (9). For patients who progress in the brain despite treatment with systemic agents or have symptomatic metastases at initial diagnosis of metastatic disease, local treatment options include surgery, SRS and WBRT. WBRT is generally recommended for patients with multiple brain metastases not suitable for surgery and/or SRS that have demonstrated some melanoma resistance to systemic therapy (10). In the past few years, at our institutions, selected patients received WBRT after multidisciplinary team discussion considering various patient and tumour factors. The use of WBRT must be balanced against the potential benefits and toxicity (9). Anecdotally, some patients have sustained response after WBRT. The aim of the study was therefore to report the outcome of WBRT in the era of systemic therapy with intracranial activity. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/tro-21-6).

Methods

Study design, inclusion and exclusion criteria

This was a retrospective cohort study of patients from Melanoma Institute Australia who underwent WBRT for MBM at three centres (Mater Hospital, Westmead Hospital, Nepean Hospital) between 2011 and 2018. Patients were eligible if they underwent WBRT concurrently or after progression with immune checkpoint inhibitor (anti-CTLA4 inhibitor, anti-PD1 inhibitor) and/or BRAF/MEK targeted therapy. Patients who received no systemic treatment or who did not complete the whole course of WBRT were excluded. This study was approved by the institutional ethics committee (approval number MIA2019/262) and individual consent for this retrospective analysis was waived. The study was performed in accordance with the tenets set forth in the Declaration of Helsinki (as revised in 2013) and Good Clinical Practice guidelines.

Patient characteristics captured included Eastern Cooperative Oncology Group (ECOG) performance status, total number of brain metastases and BRAF mutation status. Additional treatment characteristics included surgical resection, SRS, and type of systemic therapies (BRAF inhibitor, anti-PD 1, ipilimumab, and none). The RT fractionation schedule and the use of hippocampal avoidance WBRT and simultaneous integrated boost to larger lesions technique were at the discretion of the treating radiation oncologists. Patients were followed clinically with the treating clinician at 3-weekly to 3-monthly intervals. In general, MRI of the brain and CT and/or PET of the body were performed at baseline and every three months following treatment. During follow-up, the proportion of intracranial failure was determined by MRI.

Statistical analysis

Patients' characteristics were summarised using frequency and proportion or median and range as appropriate. The clinical outcomes investigated include intracranial failure and overall survival (OS). Intracranial failure was defined as intracranial progression determined by MRI. Follow up time and OS were measured from the first date of WBRT treatment until death or last follow up dates. Patients who did not experience the outcome were censored at their last follow-up date. Survival of patients during follow-up was described using Kaplan-Meier method stratified by group. Difference in survival between groups was assessed through the log-rank test.

To evaluate the impact of the current state-of-the-art systemic therapies individually, the cohort was furthermore divided into patients treated 2010–2015 and 2016–2018 and baseline and treatment characteristics as well as survival outcomes reported separately.

The following groups were considered: Concurrent WBRT and systemic therapy versus systemic therapy sequentially following completion of WBRT versus WBRT after drug failure in the brain (BRAF wild type *vs.* BRAF mutant tumor genotypes); prior neurosurgery (yes *vs.* no), prior SRS (yes *vs.* no), concurrent simultaneous integrated boost (yes *vs.* no), age (≤65 *vs.* >65 years), gender, leptomeningeal disease (yes *vs.* no), ECOG status (0–1 *vs.* ≥2), neurological symptoms (yes *vs.* no) and

Table 1 Characteristics of patients at baseline

Characteristics	N (n=90)	%
Gender		
Male	59	66
Female	31	34
Age at the diagnosis of MBM, years		
Median [range]	63 [31–84]	
<65	52	58
≥65	38	42
ECOG performance status		
0	26	29
1	47	52
2	14	16
3	3	3
BRAF mutation		
Yes	42	47
No	48	53
Leptomeningeal disease		
Yes	21	23
No	69	77
No. of metastases		
1	4	6
2–3	6	9
4–9	18	26
≥10	41	59
Neurological symptoms		
Yes	50	56
No	40	44

MBM, melanoma brain metastases.

number of metastasis (1–3 *vs.* 4–9 *vs.* ≥10). Univariable and multivariable Cox regression were performed to evaluate the association between OS and baseline factors. The final multivariable model was obtained using a stepwise backward selection on the initial models that included fractionation schedule and variables with a P value <20% from the univariate analysis (11). Two-sided P values <0.05 were considered significant. All statistical analyses were performed using SPSS ver. 21 (IBM SPSS Statistics; IBM Corporation, Armonk, New York, USA), Prism Version 8 (GraphPad Software, Inc., San Diego, CA, USA) and R version 3.6.1 (R Core Team, Vienna, Austria).

Results

Patient characteristics

A total of 106 patients who underwent WBRT between 2011 and 2018 were identified. Patients who did not receive any systemic therapy (n=8) and those who did not complete WBRT due to clinical deterioration (n=8) were excluded. Thus, the final analysis included 90 patients (*Table 1*). The median age at the time of the diagnosis of brain metastases was 63.0 years (range, 31–84) and 59 patients (66%) were males. The majority had had an ECOG performance status 0 (26 patients, 29%) to 1 (47 patients, 52%). Fifty patients (56%) had neurological symptoms at the beginning of WBRT.

Twenty-one patients (23%) had leptomeningeal disease as well as parenchymal metastasis. Of the remaining 69 patients (77%), 41 patients (59%) had 10 or more MBM, while 18 patients (26%) had 4– 9 MBM and 10 patients (15%) had 1–3 MBM. Of the 10 patients with 1–3 MBM, nine (90%) had previous surgery or SRS to the brain metastases and WBRT was given in a salvage setting after progression or in adjuvant setting on a clinical trial (9), and one patient was unwell with neurological symptoms.

Treatment details

WBRT

The prescribed dose of the WBRT ranged from 20 to 30 Gy with a mean dose of 28.8 Gy and with median fractions of 10 (range, 5–15 fractions, *Table 2*). Seventy-nine patients (88%) received 30 Gy in 10 fractions. Twenty-eight patients (31%) received hippocampal-avoidance WBRT. Concurrent simultaneous integrated boost (SIB) with WBRT was given in 27 patients (30%) with a mean total dose of 43 Gy (range, 34–63 Gy) in median fraction of ten (range, 5–15 fractions).

Systemic therapy

A breakdown of systemic therapy in WBRT-treated patients is provided in *Figure 1*. Twenty patients (22%) had first-line systemic therapy concurrently with WBRT at the presentation of MBM. These patients had a median ECOG of 1 (range, 0–3). One patient had 1 MBM, four patients had 2–3 MBM and two patients had 4–9 MBM, while 13

Table 2 Characteristics of the non-systemic treatment of patients

Characteristics	Total(n=90)	Second procedure	Third procedure
Whole brain radiation therapy			
Mean total dose, Gy [range]	28.8 [20–30]		
Median fractions [range]	10 [5–15]		
Neurosurgery			
Before WBRT, No.	28 (31%)	2 (2%)	1 (1%)
After WBRT, No.	6 (7%)	1 (1%)	0
Concurrent SIB with WBRT, No.	27 (30%)		
Median number of lesions [range]	3 [1–10]		
Mean SIB dose, Gy [range]	43 [34–63]		
Median fractions [range]	10 [5–15]		
Stereotactic radiosurgery			
Before WBRT, No.	15 (17%)	5 (6%)	1 (1%)
Median lesions [range]	2 [1–3]	1 [1–3]	3
Mean total dose, Gy [range]	19.5 [14–27]	21 [18–27]	20
Median fractions [range]	1 [1–3]	1 [1–3]	1
After WBRT, No.	8 (9%)	2 (2%)	
Median lesions [range]	5 [1–40]	1.5 [1–2]	
Mean total dose, Gy [range]	19.5 [13–27]	19 [18–20]	
Median fractions [range]	1 [1–3]	1	

WBRT, whole brain radiation therapy.

patients had 10 or more MBM.

Fifty-eight patients (64%) progressed on systemic therapy in the brain prior to WBRT (*Table 3*) and had a median ECOG of 1 (range, 0–3). Nine patients (16%) did not have any further systemic therapy after WBRT, 49 patients (84%) had further systemic therapy. These included further immunotherapy in 38 patients (78%), targeted therapy in 10 patients (20%), and clinical trial participation in one patient (2%).

In 12 patients (13%), systemic therapy was administered sequentially following completion of WBRT. These patients had a median ECOG of 1 (range, 0–2) and two patients had one MBM, five patients had four to nine MBM, while five patients had 10 or more MBM.

Surgery and SRS

Fifteen patients (17%) had SRS prior to WBRT with a median number of treated lesions of two (range, 1–3 lesions), with a mean total dose of 19.5 Gy (range, 14–27 Gy) in median of one fraction (range, 1–3 fractions). Of those, five patients received a second course and one patient a third course of SRS. These patients had a median age of 61 and a median time between SRS and WBRT of five months (range, 0–22 months). Twenty-eight patients (31%, median age 63.5 years) underwent surgery of MBM before WBRT, while two patients had a second operation and one patient a third operation. The median time between surgery and WBRT was 1 month (range, 0–27 months). In all patients, surgery was performed for symptomatic disease.

Eight patients (9%, median age 63 years)) had SRS after WBRT with a median number of treated lesions of five (range, 1–40 lesions), and a mean total dose of 19.5 Gy (range, 13–27 Gy) in median of one fraction (range, 1–3 fractions). The median time between WBRT and subsequent SRS was 5 months. Two patients received

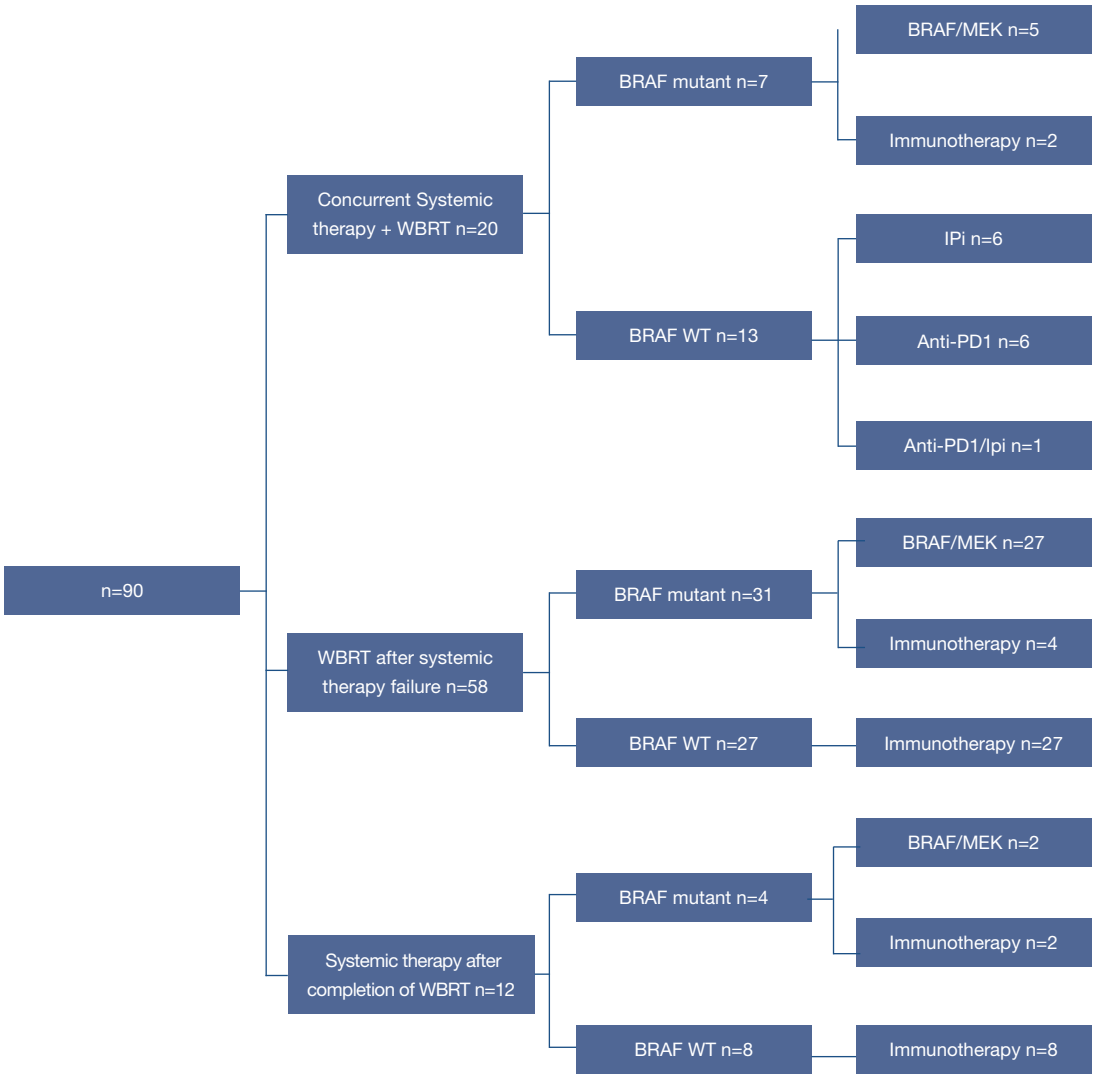

Figure 1 Details of the whole cohort regarding systemic therapy prior to WBRT. WBRT, whole brain radiation therapy.

Table 3 Details of systemic treatment prior to WBRT

Variable	BRAF/MEK inhibitors	Anti-PD1	Ipilimumab	Anti-PD1 and ipilimumab	Clinical trial	Total
BRAF mutant type (n=42)						
Prior systemic therapy (1st line)	27	2	0	2	0	31
Prior systemic therapy (2nd line)	4	5	3	3	0	15
BRAF wild type (n=48)						
Prior systemic therapy (1st line)	0	15	8	4	0	27
Prior systemic therapy (2nd line)	0	4	2	2	1	9

WBRT, whole brain radiation therapy.

a second course of SRS. Six patients (7%, median age 67.5 years) underwent surgery after WBRT (four for progressive MBM and two for radionecrosis) and one patient had a second operation. The median time between WBRT and surgery was 9 months (range, 2–22 months).

Outcomes

The median follow-up was 4.5 months (range 0–64). At the time of analysis, death was reported for 75 patients (83%). The median OS from diagnosis of MBM was eight months (range, 1–83 months) and the median OS from the beginning of WBRT was 5 months (range, 0–64 months). The 12 months OS from WBRT was 28% (*Figure 2A*). Details on WBRT timing and systemic therapy for 12-month survivors are provided in Figure S1. Fifty-three patients (59%) had a follow-up MRI, while the remaining patients had progressive disease. Twenty-eight of these patients (53%) showed progression of existing MBM or developed new intracranial lesions at a median time of 8 months.

On univariate analysis, the presence of a BRAF mutation did not result in a statistically significant difference in median survival (P=0.41). Patients with BRAF mutant disease who had prior systemic treatment (n=31) had a median survival from WBRT of 4.6 months versus those with BRAF wild type disease (n=27) with a median survival of 5.2 months; patients with no systemic treatment prior to WBRT (n=32) had a median survival of 6.7 months. There was no significant difference between these three groups (P=0.65, *Figure 2B*). Prior brain directed local therapy (surgery or SRS) was associated with better survival. The median survival for those who had prior surgery was 12 months compared with four months for those who did not have prior surgery (P=0.0023, *Figure 2C*). Similarly, those who had prior SRS showed statistically significantly longer survival (18 *vs.* 8 months median survival time, P=0.0245, *Figure 2D*). Those who had neurological symptoms at the time of WBRT had poorer survival (median OS 5 *vs.* 7 months, *Figure 2E*).

In the multivariable analysis (*Table 4*), the presence of neurological symptoms was associated with worse OS from time of WBRT (P=0.029). Prior surgery remained significantly associated with better OS (HR 0.42, 95% CI: 0.24, 0.73, P=0.002) but not prior SRS (HR 0.51, 95% CI: 0.24, 1.08, P=0.079). WBRT with concurrent SIB did not improve the survival significantly (median survival 4 months without concurrent SIB versus 8 months with SIB, P=0.12). Factors such as age, gender, ECOG status, BRAF mutation status, number of MBM, and leptomeningeal disease did not influence the OS.

Impact of timing of systemic therapy

Kaplan-Meier plots, patient and treatment characteristics by the study period (2010–2015 *vs.* 2016–2018) are provided in Figure S2 and Tables S1-S3. There was no statistically significant difference in outcomes between the two study periods. However, patients treated 2010–2015 showed a significantly better ECOG status (ECOG 2–3, 9%) than patients treated 2016–2018 (ECOG 2–3, 32%, P=0.006).

Discussion

Multidisciplinary team management of patients with melanoma is recommended by expert bodies (10,12,13). The management of MBM is carefully discussed by a melanoma multidisciplinary team including medical oncologists, radiation oncologists and neurosurgeons. In this selected cohort of 90 patients who were recommended to have WBRT in the era of systemic therapy with known intracranial activity, the median survival was 8 months from the initial diagnosis of MBM. Our study resulted in several main findings relevant for clinical practice in the management of MBM. Patients who underwent prior surgery or had no neurological symptoms demonstrated significantly better survival. On the other hand, the BRAF status and the type of systemic therapy prior to WBRT did not significantly influence survival. In the 21 patients who had leptomeningeal disease, they did not appear to have a worse survival compared to those with parenchymal MBM.

The OS of this cohort is favourable compared to studies prior to the availability of immunotherapy and targeted therapy, reporting a median OS in the range of 4–6 months after the diagnosis of MBM (3,14-16). Despite 64% of patients having progressed in the brain on BRAF/MEK inhibitors and/or immune checkpoint inhibitors prior to WBRT, the median OS was 5 months and the 12-month survival rate was 28% after WBRT. In multivariate analysis, prior neurosurgery was statistically significantly associated with better OS. Neurosurgery is generally indicated in patients with symptomatic MBM due to dominant lesions and in patients with better performance status and lower burden of intracranial and extracranial disease. In a previous study of mixed histologies, concomitant SRS was associated with improved survival over WBRT alone with a median

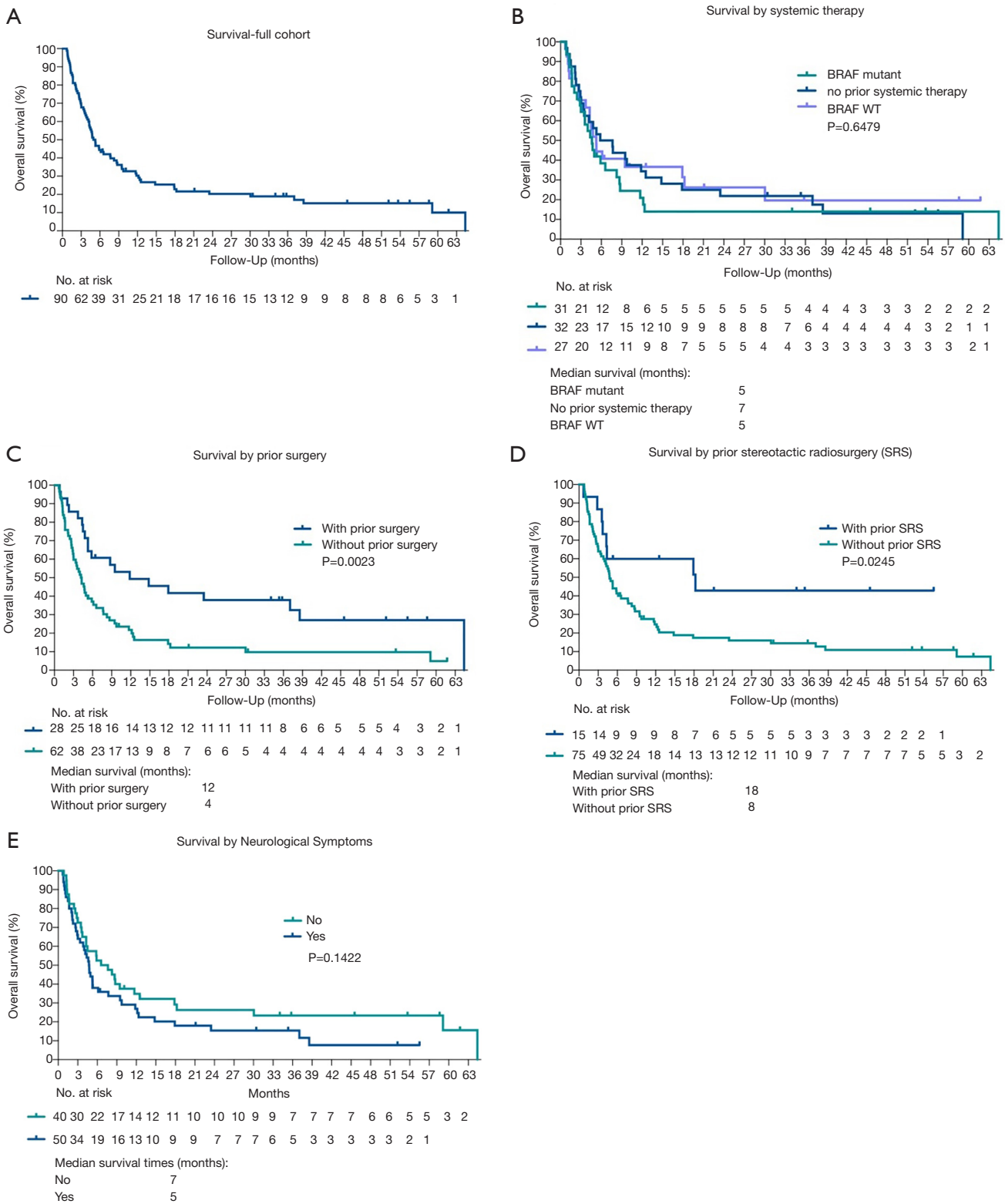

Figure 2 Survival outcomes in the full cohort from time of WBRT (A), by systemic therapy (for BRAF mutant, for no prior systemic therapy, for BRAF wild type) (B), prior surgery (C), prior stereotactic radiosurgery (D) and by neurological symptoms (E). WBRT, whole brain radiation therapy.

Table 4 Univariable and multivariable regression of overall-survival from time of WBRT

Variable	Univariable		Multivariable*	
	HR	P value	HR	P value
Age at diagnosis of MBM				
<65	1	0.9847		
≥65	1.00 (0.63, 1.59)			
Gender				
Female	1	0.1841		
Male	0.73 (0.45, 1.16)			
Leptomeningeal disease				
No	1	0.1461		
Yes	1.48 (0.87, 2.49)			
ECOG				
0–1	1	0.3876		
≥2	1.29 (0.72, 2.32)			
Neurological symptoms				
No	1	0.1447	1	0.0286
Yes	1.4 (0.88, 1.41)		1.72 (1.05, 2.78)	
Number of MBM				
1–3	1	0.0151		
4–9	1.68 (0.63, 4.52)			
≥2	2.96 (1.26, 6.94)			
Prior neurosurgery				
No	1	0.0030	1	0.0020
Yes	0.45 (0.26, 0.76)		0.42 (0.24, 0.73)	
Prior SRS				
No	1	0.0288	1	0.0798
Yes	0.44 (0.21, 0.92)		0.51 (0.24, 1.08)	
Prior systemic therapy				
No prior systemic therapy	1	0.6512		
BRAF mutant with prior systemic therapy	1.21 (0.71, 2.08)			
BRAF wild type with prior systemic therapy	0.94 (0.53, 1.67)			

*, derived using a backward model selection. Initial model included all variables with P value <0.20. WBRT, whole brain radiation therapy.

survival time of 6.5 versus 4.9 months (17). Kocher *et al.* reported no statistically significant impact of adjuvant WBRT versus observation in patients treated with prior surgery or SRS with a median survival of 10.9 versus 10.7 month (18). Both studies included only patients with one to three brain metastases and mainly patients with lung and breast cancer (where drugs have little intracranial activity), with only a few patients with melanoma. In our study, the majority of patients had more than three or even more than 10 brain metastases and received WBRT as a last-

line palliative therapy. On the other hand, surgery and SRS were associated with better survival, but those patients who had no prior surgery or SRS presumably had either brain metastasis too extensive for SRS or surgery, or poorer performance status, which may explain the worse survival in those who did not have prior surgery or SRS.

The indication for WBRT in combination with other modalities is complex, and must be considered in the light of recent advances in systemic therapies that can be effective in patients with MBM. For asymptomatic patients, ipilimumab has shown an intracranial response rate of 5–16% (19) and pembrolizumab or nivolumab alone achieved a response rate of 21–22%, and 46–56% with the combination of ipilimumab and nivolumab (6,20). BRAF inhibitors are also known to be effective in MBM with intracranial response rates of 39% for dabrafenib and 29% for vemurafenib alone (21,22), while the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib achieved response rates of 58% 5. Therefore, in patients with asymptomatic, untreated MBM, systemic therapy (particularly immunotherapy) can be considered as first line treatment (as an alternative to local brain therapy) with multidisciplinary support from a radiation oncologist and a neurosurgeon.

Our study adds outcome data of a large cohort of patients with MBM treated with WBRT in addition to systemic therapies. Our results indicate that patients with BRAF mutant disease receiving targeted therapy prior to WBRT had similar survival outcomes compared to patients with BRAF wild type receiving prior immunotherapy. Previous studies have investigated the combination of ipilimumab and WBRT mainly in the setting of safety evaluations (23-26) and showed similar survival results in the range of 3.1–8.5 months, compared to our study. Regarding targeted therapy and WBRT, prior research showed median survival times of 4.6 months (27) which is also in line with our results. Concerning the timing of WBRT in relation to systemic therapy, patients receiving systemic treatment after WBRT had a slightly improved, but not statistically significantly better OS of 6.7 months. In prior studies, patients receiving systemic therapy initially at the start of or shortly after radiation treatment showed an additive effect of radiation therapy and systemic therapy (26,28-31) which was however not the case in our study. This discrepancy could be explained by the fact that prior studies used SRS instead of WBRT, which may trigger additional anti-tumor immune response.

It is important to note that medical therapy of MBM is an actively evolving field that has changed substantially in the recent years. In particular, systemic therapy with intracranial activity such as the combination of ipilimumab and anti-PD1 only became routinely available outside clinical trial setting in Australia in 2017. It is therefore not surprising to note that, when analysed separately, the cohort of patients treated from 2016 onwards had a significantly worse baseline ECOG performance status than patients treated earlier. In this era of modern systemic therapy, WBRT was restricted to patients with aggressive disease and/or who had already progressed previously. With state-of-the-art treatment, these patients with unfavourable prognosis had similar outcome after WBRT compared to patients with a more favourable disease condition several years ago.

Our main limitations were the retrospective design of our study, conferring risk of selection bias, and the lack of subgroup analysis regarding specific types of systemic treatments due to small numbers. A further limitation includes the lack of standardized reporting of toxicity of WBRT such as neurocognitive decline or radionecrosis.

In conclusion, in patients with MBM treated with systemic therapy with known intracranial activity, WBRT was used in our cohort in addition to surgery and SRS in selected patients. Future studies in a prospective randomized design should determine toxicity, quality of life and the sequencing of systemic treatment with RT in patients with MBM, particularly in patients with multiple brain metastases.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/tro-21-6

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tro-21-6). GVL received Salary support from NHMRC fellowship and the University of Sydney Medical Foundation, travel support from Bristol Myers Squibb, Novartis, Roche, Amgen, Pierre Fabre, MERCK and Array. She also received Consultancy fees from Bristol Myers Squibb, Novartis, Roche, Amgen, Pierre Fabre,

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee (approval number MIA2019/262) and individual consent for this retrospective analysis was waived.

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Supplementary

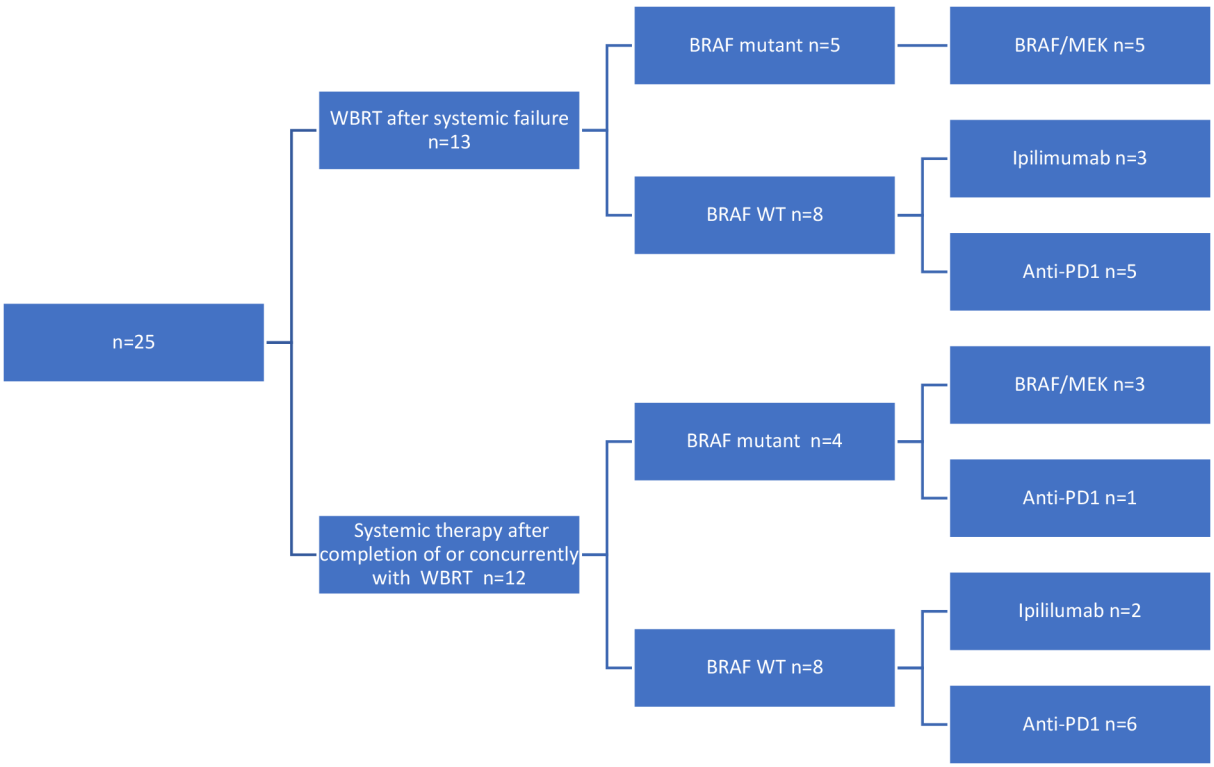

Figure S1 Details on systemic therapy for 12-month survivors.

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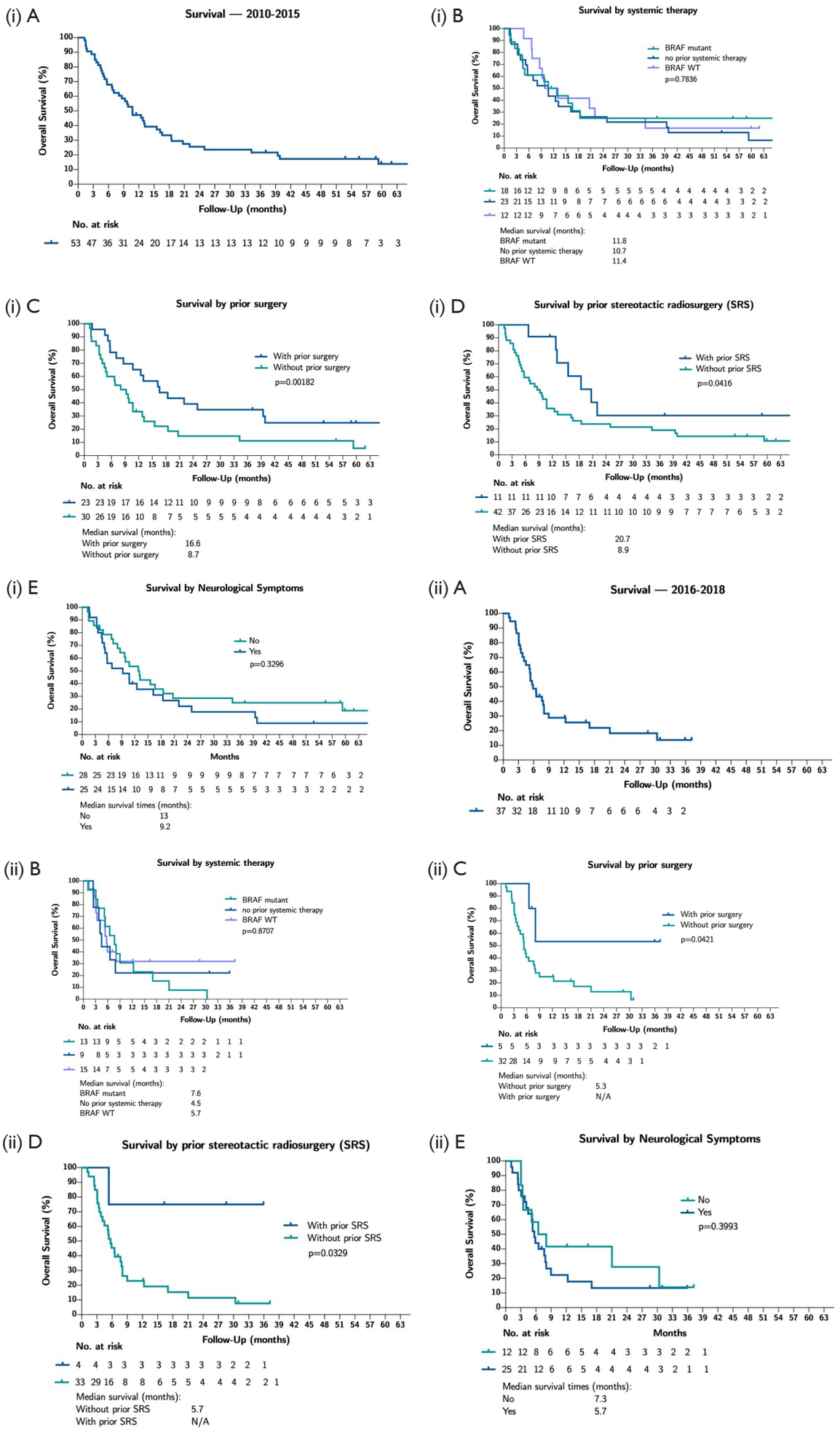

Figure S2 Survival outcomes in patients with WBRT between 2010-2015 (i) and 2016-2018 (ii) (A), by systemic therapy (for BRAF mutant, for no prior systemic therapy, for BRAF WT) (B), prior surgery (C), prior stereotactic radiosurgery (D) and by neurological symptoms (E), respectively.

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Table S1 Characteristics of Patients at Baseline at WBRT start by the timing of systemic therapy (2010–2015 *vs.* 2016–2018)

Characteristics	A 2011-2015		B 2016-2018	
	N (n=53)	%	N (n=37)	%
Gender				
Male	36	68	23	62
Female	17	32	14	38
Age at the Diagnosis of MBM, years				
Median (range)	63 (34-80)		62 (31-84)	
<65	31	58	21	57
≥65	22	42	16	43
ECOG performance status				
0-1	48	91	25	68
2-3	5	9	12	32
BRAF mutation				
Yes	26	49	16	43
No	27	51	21	57
Leptomeningeal disease				
Yes	11	21	10	27
No	42	79	27	73
No. of metastases				
1	4	9.5	0	0
2-3	4	9.5	2	7
4-9	11	26	7	26
≥10	23	55	18	67
Neurological symptoms				
Yes	25	47	25	68
No	28	53	12	32

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Table S2 Characteristics of the non-systemic treatment of patients (2011-2015)

Characteristics	Total (n=53)	Second procedure	Third procedure
Whole-brain radiation therapy			
Mean total dose, Gy (range)	29.6 (20-30)		
Median fractions (range)	10 (5-15)		
Neurosurgery			
Before WBRT, No.	23 (43%)	2 (4%)	1 (2%)
After WBRT, No.	6 (11%)	1 (2%)	0
Concurrent SIB with WBRT, No.	16 (30%)		
Median number of lesions (range)	4 (1-10)		
Mean SIB dose, Gy (range)	46 (40-63)		
Median fractions (range)	10 (5-15)		
Stereotactic radiosurgery			
Before WBRT, No.	11 (21%)	3 (6%)	1 (2%)
Median lesions (range)	2 (1-3)	1 (1)	3
Mean total dose, Gy (range)	18.8 (14-22)	19.3 (18-20)	20
Median fractions (range)	1 (1)	1 (1)	1
After WBRT, No.	6 (11%)	2 (4%)	
Median lesions (range)	5 (2-40)	1.5 (1-2)	
Mean total dose, Gy (range)	18.6 (13-24)	19 (18-20)	
Median fractions (range)	1 (1-3)	1	

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Table S3 Characteristics of the non-systemic treatment of patients (2016-2018)

Characteristics	Total (n=37)	Second procedure
Whole-brain radiation therapy		
Mean total dose, Gy (range)	27.6 (20-30)	
Median fractions (range)	10 (5-15)	
Neurosurgery		
Before WBRT, No.	5 (14%)	
After WBRT, No.	2 (5%)	
Concurrent SIB with WBRT, No.	11 (30%)	
Median number of lesions (range)	3 (3-5)	
Mean SIB dose, Gy (range)	40 (34-45)	
Median fractions (range)	10 (10-15)	
Stereotactic radiosurgery		
Before WBRT, No.	4 (11%)	2 (5%)
Median lesions (range)	2 (1-2)	1 (1-3)
Mean total dose, Gy (range)	21.8 (20-27)	23.5 (20-27)
Median fractions (range)	1 (1-3)	1 (1-3)
After WBRT, No.	2 (5%)	
Median lesions (range)	1 (1-10)	
Mean total dose, Gy (range)	25.5 (24-27)	
Median fractions (range)	3 (3)	

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