

Leukoencephalopathy after Whole Brain Radiation Therapy Plus Radiosurgery Versus Radiosurgery Alone for Metastatic Melanoma to the Brain

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Abstract

Advances in the treatment of melanoma with novel systemic therapies have meaningfully increased survival of patients. The brain is a common early site for melanoma metastases. Whole-brain radiation therapy (WBRT) is of limited effectiveness for radioresistant histologies such as melanoma and has been associated with white matter change and cognitive dysfunction. Prior studies of leukoencephalopathy after treatment with WBRT and/or stereotactic radiosurgery (SRS) have focused on pathologies where chemotherapy is reflexively used in the majority of patients. The study's aim was to evaluate the risk of leukoencephalopathy in patients with melanoma brain metastases receiving SRS and WBRT versus SRS alone. We retrospectively reviewed 63 patients who underwent SRS with or without WBRT between April 1988 and December 2012. The study's aim was to evaluate the risk of leukoencephalopathy in patients with melanoma brain metastases receiving stereotactic radiosurgery and whole-brain radiation therapy versus SRS alone. We retrospectively reviewed 63 patients who underwent SRS with or without WBRT between April 1988 and December 2012. Degree of leukoencephalopathy was evaluated on T2 and FLAIR MRI sequences using a simple, previously-described method. A significantly lower proportion of patients treated with SRS developed leukoencephalopathy in long-term follow up compared to patients treated with SRS and WBRT. This study demonstrates an increased risk of leukoencephalopathy following WBRT compared to SRS alone in a cohort of melanoma brain metastases patients with a low rate of treatment with alkylating chemotherapeutic agents.

Keywords: Stereotactic radiosurgery; Whole brain radiation therapy; Brain metastasis; Gamma Knife; Leukoencephalopathy; Melanoma

Introduction

Melanoma is the third leading cause of metastatic disease to the brain, behind only lung and breast cancer, and metastatic melanoma brain lesions have historically portended a poor prognosis [1-3]. Melanoma has the highest likelihood of all primary tumors to metastasize to the brain and the brain is often the first visceral site of metastases [4,5]. Between 20% to 50% of patients with metastatic melanoma will die due to brain metastases [6]. Whole-brain radiation therapy (WBRT) has been used reflexively for many years as the primary treatment for metastatic brain cancer. Outcomes of treatment with WBRT have not significantly changed despite changes in dosing, fractionation schedules, or the use of radiosensitizers [7-10]. In addition, melanoma is a radioresistant histology for which conventional fractionated radiation therapy is less effective [11-13]. Stereotactic radiosurgery (SRS) is a proven, minimally invasive treatment modality for brain metastasis, including melanoma [14-21]. The addition of WBRT to locally-targeted therapies like surgery or SRS for brain metastases has not proven to increase survival or quality of life [22-25]. However, the addition of SRS to WBRT does improve survival, which calls into the question the need for WBRT [19,26].

The neurotoxic effects of WBRT have been difficult to study due to the previously short life expectancies of patients with brain metastases. This has been especially true in melanoma. However, earlier diagnosis and more effective systemic therapies such as immunotherapy with BRAF inhibitors and anti-CTLA-4 monoclonal antibodies have

improved survival for patients with metastatic melanoma [27-30]. Treatment of metastatic melanoma is differentiated from treatment of breast and lung cancer by less frequent use of chemotherapy and a stronger emphasis on immunotherapy due to higher and more durable response rates [28-33]. WBRT appears to cause neurotoxicity through a variety of mechanisms including small cerebral vasculature damage with resultant local edema, destruction of oligodendrocytes and the subependymal stem cell population [34-37]. White matter damage visible on neuroimaging has been correlated with neurocognitive dysfunction in Alzheimer's dementia, alcohol abuse, inborn errors of metabolism, and numerous other diseases [38-40]. We previously demonstrated that in a lung cancer cohort that the use of WBRT for brain metastases induces irreversible, progressive leukoencephalopathy [41]. Likewise, WBRT negatively effects cognition, memory, and mood [42,43].

This retrospective study in longer-term survivors of metastatic melanoma to the brain was designed to evaluate the risk of developing leukoencephalopathy after treatment with WBRT plus SRS versus SRS alone. We sought to distinguish this investigation from our previous studies of leukoencephalopathy by studying a cohort of patients with low rates of treatment with alkylating chemotherapeutic agents.

Methods

Patient population

With Institutional Review Board approval, we retrospectively reviewed data from 446 consecutive patients who underwent Gamma

Knife SRS for melanoma brain metastases between April 1988 and December 2012. Sixty-three patients with evaluable imaging obtained at baseline and approximately 1 and 2 years after WBRT or initial SRS were included. Forty-nine patients who underwent SRS alone were compared with 14 patients who underwent WBRT plus SRS. Demographic data including age, sex, previous chemotherapy or immunotherapy, previous extracranial radiation, dose and fractions of WBRT, number of metastases treated by SRS, SRS margin dose, and gross tumor volume were evaluated.

WBRT and SRS treatment protocol

WBRT was typically administered at outside hospitals closer to patients' homes. Details of treatment were obtained from outside facilities' records if the patient did not receive WBRT at our facility. Median total dose was 30 Gy (range=30 to 35 Gy). The median number of fractions was 12 (range=12 to 18 fractions). No patient had repeat WBRT during the evaluation period. The WBRT completion date was the time from which imaging follow-up was calculated for that cohort. Twelve of the 14 patients in the WBRT plus SRS cohort received SRS following WBRT for either boost treatment or delayed salvage therapy.

In patients who received SRS alone, imaging follow-up was calculated from the date of the first SRS procedure. All patients had at least one Gamma Knife radiosurgical procedure. Patients who

underwent WBRT had a median of one SRS treatment (range 1-4), while patients treated with SRS only had a median of two SRS procedures (range 1-9). Our radiosurgical technique has been described [19]. Referred patients are candidates for SRS in the absence of: symptomatic mass effect requiring surgery, miliary brain metastases, or carcinomatous meningitis.

Imaging evaluation

Patients were followed with magnetic resonance imaging (MRI) serially. MRIs were scored at a median of one and two years post treatment with a qualitative grading scale allowing for a simple and rapid evaluation that reflects the centrifugal progression of radiation-induced white matter change originating at periventricular white matter [41].

White matter changes were assessed using T2 or FLAIR (fluid attenuated image recovery) MRI sequences: grade 1=little or no white matter hyperintensity; grade 2=limited periventricular hyperintensity; and grade=diffuse white matter hyperintensity.

Local white matter change due to tumors or surgical intervention was not incorporated. Figure 1 shows MR images representative of each grade. The MRIs were evaluated by authors blinded to the details of patient treatments (P.C. and E.M.).

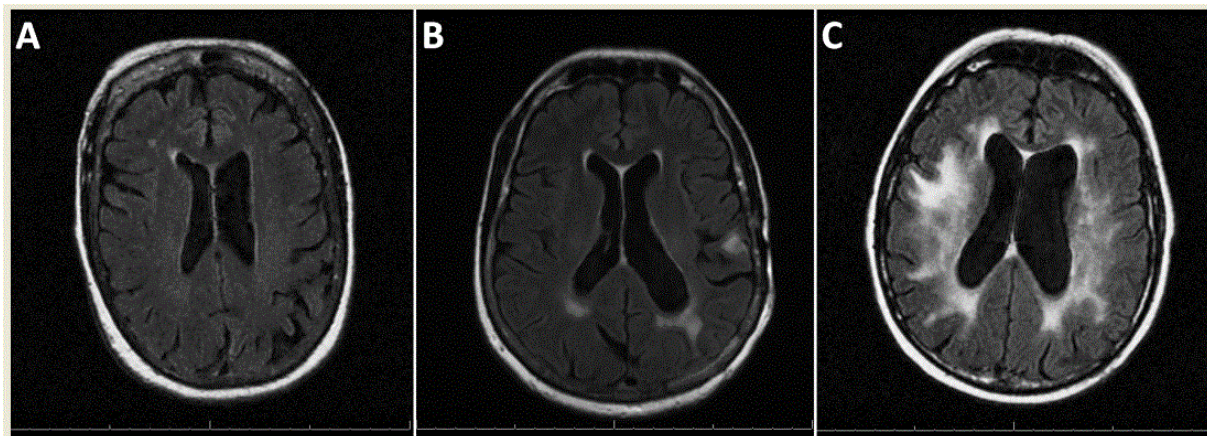


Figure 1: Representative FLAIR images showing typical (A) grade 1, (B) grade 2, and (C) grade 3 leukoencephalopathy.

Statistical analyses

Normally distributed data are presented as means and standard deviations. Non-normally distributed data are presented as medians and interquartile ranges.

Variables pertaining to the two groups were compared with appropriate statistical tests to identify significant differences (Stata version 13.1; StataCorp, College Station, TX). Student t-test was used for normally distributed continuous data, and the Wilcoxon rank-sum test was used for nonparametric, non-normally distributed continuous data.

The Pearson chi-square test was used for categorical data, and the Fisher exact test was used for categorical data when the cells had an expected count of less than five. A p-value less than 0.05 was considered statistically significant.

Results

Patient characteristics

The baseline characteristics of the two cohorts were similar (Table 1). No significant difference was found between the two cohorts in the rate of chemotherapy treatment (WBRT+SRS 50%, SRS only 31%, $p=0.31$). Overall, 35% of patients had chemotherapy. The number of metastases initially treated (median of 3 vs 1, $p=0.05$), the total number of tumors treated (median of 3.5 vs 5, $p=0.68$), and the total volume of treated tumors (7.8 cc vs 6.9 cc, $p=0.51$) were not significantly different.

However, patients in the SRS alone cohort underwent significantly more SRS procedures over their clinical course (median 2 vs 1, $p=0.013$). The SRS marginal tumor dosing was lower for the WBRT

plus SRS cohort versus the SRS only cohort (16 Gy vs 20 Gy, respectively, $p=0.0001$).

This reflects our practice of routinely lowering the SRS prescription dose for patients who have undergone previous WBRT. The median

survival for patients receiving SRS-only was more than double that of the combination group (24.0 months vs 11.3 months, $p=0.0007$). Ten of the patients treated with SRS-only were still alive at the time of data analysis.

Characteristic	WBRT + SRS	SRS Only	p-value
Total, n=63	n=14	n=49	
Age, Mean (standard deviation)	59.7 (13.3)	57.9 (11.7)	0.62 ^a
Male	10 (71.4%)	34 (69.4)	1.00 ^c
Prior chemotherapy	7 (50.0%)	15 (30.6%)	0.31 ^b
Prior extracranial radiation	0 (0.0%)	6 (12.2%)	0.39 ^b
SRS treatments Median (range)	1 (1-4)	2 (1-9)	0.01 ^d
Total Mets treated by SRS Median (range)	3.5 (1-29)	5 (1-41)	0.68 ^d
Mets treated at initial SRS Median (range)	3 (1-11)	1 (1-8)	0.0501 ^d
Tumor volume treated, cc Median (range)	7.8 (1.2-32.4)	6.9 (0.4-40.8)	0.51 ^d
Survival, mo Median (range)	11.3 (2.9-107.0)	24.0 (10.9-118.5)	0.0007 ^d
Marginal SRS dose, Gy Median (range)	16 (15-20)	20 (14-22)	0.0001 ^d
Proximity of baseline MRI to treatment, months Median (range)	0.8 (-0.7-4.4)	0.0 (-1.0-2.8)	0.13 ^d
Time to first graded imaging, months Median (range)	11.2 (6.8-20.2)	12.2 (9.6-14.9)	0.20 ^d
Time to second graded imaging, months Median (range)	23.9 (21.4-29.2)	24.4 (22.7-29.4)	0.67 ^d

Caption: Mets indicates metastases; MRI: Magnetic Resonance imaging; SRS: Stereotactic Radiosurgery; WBRT: Whole-Brain Radiation Therapy.

*indicates significant value.

^aBased on student t-test

^bBased on Pearson chi-square test

^cBased on Fisher exact test

^dBased on Wilcoxon rank-sum test

Table 1: Baseline characteristics of the study cohorts.

Imaging results

Both patient cohorts had similar initial white matter grades (Table 2). At the one year imaging evaluation (median time after treatment of 11.2 and 12.2 months, respectively for WBRT plus SRS and SRS alone), a significantly higher proportion of patients who received WBRT had grades 2 or 3 leukoencephalopathy compared to patients who were only treated with SRS (71.4% vs 12.2%, respectively, $p<0.0001$).

Indeed only one of the SRS only patients showed any change in leukoencephalopathy grade after one year. At 2 years after the initial treatment (median time to second evaluated imaging 23.9 and 24.4 months, respectively, for WBRT plus SRS and SRS only), 75% of surviving patients who received WBRT showed leukoencephalopathy versus 16.7% of the surviving SRS only patients ($p=0.0458$).

No patients treated only with SRS developed grade 3 changes and only three patient developed any white matter changes during the course of follow up (Figures 2 and 3).

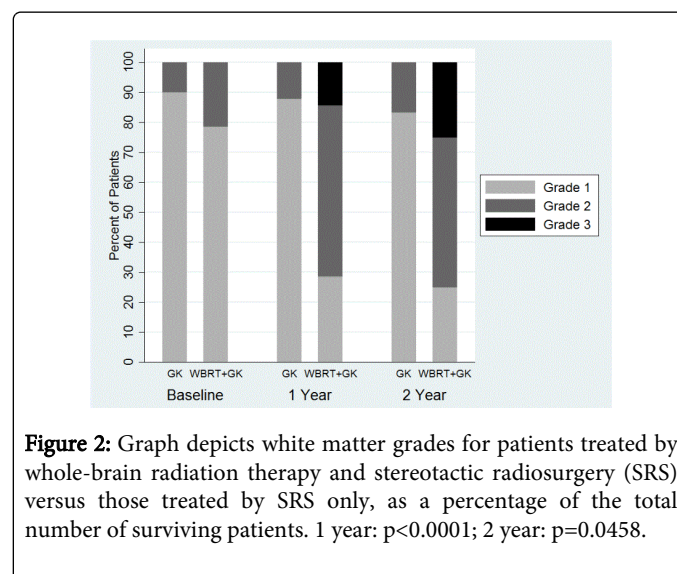


Figure 2: Graph depicts white matter grades for patients treated by whole-brain radiation therapy and stereotactic radiosurgery (SRS) versus those treated by SRS only, as a percentage of the total number of surviving patients. 1 year: $p<0.0001$; 2 year: $p=0.0458$.

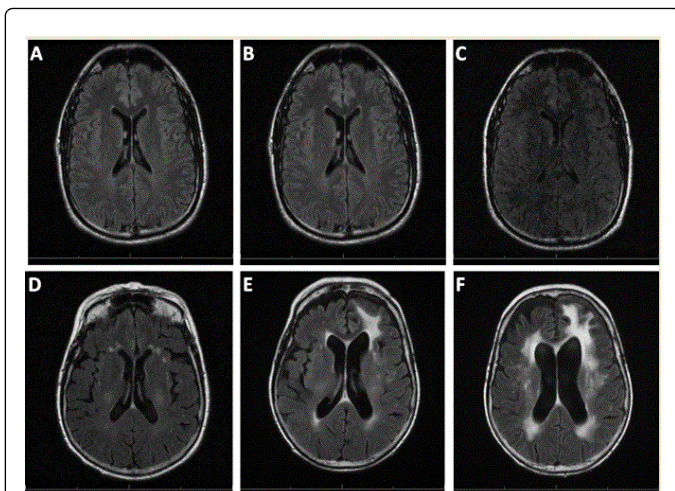


Figure 3: FLAIR images are shown for a patient at (A) baseline and at (B) 13.0 and (C) 24.5 months after initial stereotactic radiosurgery procedure, compared with those from a patient at (D) baseline and at (E) 14.1 months and (F) 25.3 months after initial whole-brain radiation therapy.

	WBRT + SRS	SRS Only	p-value
White matter score at baseline			
1	11 (78.6%)	44 (90.0%)	0.3609
2	3 (21.4%)	5 (10.0%)	
3	0	0	
White matter score at 1yr			
1	4 (28.6%)	43 (87.8%)	<0.0001
2	8 (57.1%)	6 (12.2%)	
3	2 (14.3%)	0	
White matter score at 2yr			
1	1 (25.0%)	15 (83.3%)	0.0458
2	2 (50.0%)	3 (16.7%)	
3	1 (25.0%)	0	

Table 2: White matter change following treatment for brain metastases.

Discussion

Prognosis in patients with metastatic melanoma is dependent on demographic and tumor characteristics, as well as treatment factors. The potential for extended survival in melanoma patients requires consideration of the long-term effects of treatment, particularly in patients who are more likely to have a favorable prognosis – those with limited brain disease, controlled systemic disease, without primary head and neck lesions, under the age of 65, and excellent performance status [2,44,45]. Extensive investigation is ongoing into the use of immunotherapies for treatment of metastatic melanoma. Ipilimumab,

an anti-CTLA-4 monoclonal antibody, has proven particularly promising. A study by Shoukat et al. demonstrated 28.3 months of survival from the time of initial SRS for patients receiving SRS and ipilimumab for metastatic melanoma to the brain [30]. Knisely et al. found that combining ipilimumab and SRS increased survival from time of initial SRS to 21.3 months [28]. Silk et al. investigated the combination of ipilimumab and any radiation therapy (SRS or WBRT), and found that ipilimumab increased survival to 18.3 months and SRS was a predictor for better outcome compared to WBRT [29]. The potential for significantly prolonged survival in patients with metastatic melanoma to the brain is a major paradigm change and requires a significant reconsideration of previous treatment paradigms for brain metastases in order to avoid delayed toxicities.

This investigation builds on prior work done in our group that examined differential levels of leukoencephalopathy in patients with metastatic lung and breast cancer to the brain treated with SRS and WBRT compared to SRS only [41,46]. Chemotherapy has previously been implicated in white matter change and subsequent neurocognitive dysfunction [47-49]. In the prior cohorts of patients our group studied with metastatic breast and lung cancer, 100% and 96% of patients had treatment with chemotherapy, respectively [41,46]. In contrast, only 35% of this melanoma cohort had traditional chemotherapy with no statistically significant difference between the two cohorts. The smaller proportion of patients with a history of chemotherapy in our current investigation greatly reduces, but does not eliminate the likelihood that chemotherapeutic agents are responsible for the development of leukoencephalopathy instead of differences in radiation treatment modality. Instead, it is likely that leukoencephalopathy after treatment strategies including WBRT is largely due to the WBRT component. However, one cannot rule out an additive effect of SRS with WBRT. Nevertheless, given the targeted nature of SRS, and the near complete absence of global white matter effects in the SRS only cohort, we suggest that any additive effect of SRS is minimal if any at all.

Balancing disease control and quality of life has become a growing emphasis in cancer therapy. In our series, 71.3% of patients demonstrated leukoencephalopathy at one year after WBRT. This is in agreement with previous estimates of the incidence of leukoencephalopathy following WBRT (83% to 100%) [50,51]. Leukoencephalopathy has been correlated with neurocognitive dysfunction in patients receiving WBRT for treatment of low-grade gliomas [52]. Radiation in children causes meaningful neurocognitive toxicity that can affect multiple domains of development. Supratentorial brain irradiation in children is correlated with decreased intelligence [53]. Treatment strategies have evolved to delay or withhold radiation entirely in children [54]. The delayed effects of WBRT are only beginning to be better understood in adults, likely due to the overall poor survival rates of patients with conditions requiring WBRT. In a secondary analysis of a randomized trial, Aoyama et al. found that although neurocognitive dysfunction correlated most with metastatic tumor recurrence, WBRT also caused significant neurocognitive toxicity [55]. Kondziolka et al. evaluated surveyed patients with brain metastases following WBRT plus SRS or SRS alone [43]. Patients who received WBRT reported significantly greater difficulties with short- (72% vs 16%) and long-term memory (33% vs 13%), concentration (61% vs 25%), and depression (54% vs 19%). Chang et al., in the first randomized, controlled trial with a neurocognitive primary endpoint, observed that patients who received WBRT plus SRS were at significantly higher risk for developing learning and memory dysfunction by 4 months after treatment

compared to those treated with SRS alone, despite higher tumor recurrence in the SRS only cohort [56]. Taken together with our study, these data indicate that WBRT has adverse effects on the brain, both structurally and functionally, and that withholding it in favor of SRS may prevent delayed, previously under-recognized toxicities.

Going forward it will be critical to perform studies that are designed to address the unique issues associated with a specific brain metastasis histology rather than lumping all histologies together. For instance, prognosis in breast cancer metastases patients is strongly associated with the hormonal status of the tumor [57]. However, for melanoma previous work suggests that only performance status and the number of tumors is prognostic [45]. Most previous studies in this area were fundamentally flawed when considering melanoma because they simply combined all histologies together, and often did not have many melanoma patients [23]. For example, only 2 of 95 patients had melanoma in one often cited landmark study regarding the utility of WBRT following surgery [58]. Aoyama et al. studied SRS plus WBRT vs WBRT alone, but 66% of patients had lung cancer [59]. The present study was specifically geared to assess the risk of delayed leukoencephalopathy in melanoma patients following treatment for brain metastases. It reinforces our previous work demonstrating that WBRT plus SRS significantly increases the risk of leukoencephalopathy compared to SRS alone for treatment of brain metastases from lung cancer [41]. Our study has several important limitations. It is retrospective and lacks neurocognitive and quality-of-life correlations. A multicenter, prospective trial being conducted by the North American Gamma Knife Consortium comparing WBRT plus SRS versus SRS alone for the treatment of brain metastases includes neurocognitive and quality-of-life assessments as primary outcomes in addition to an imaging assessment of leukoencephalopathy. Selection bias for long-term survivors may limit the generalizability of our findings. For example, the SRS cohort in our study demonstrated significantly greater survival, a finding that is not always observed in other studies where SRS has been shown only to be at least equivalent to WBRT plus SRS [59]. Qualitative imaging assessments lack sensitivity when compared to volumetric analyses, resulting in potential underestimation of white matter change. Despite these limitations, the significant difference between treatment groups is notable. This work adds to the evidence demonstrating the differential effects of radiation therapies on normal brain structure and function. In addition to prospectively collecting detailed neurocognitive and quality-of-life data for patients receiving SRS and/or WBRT, future avenues for investigation include radiographic assessments of brain atrophy and anatomic disruptions on high-definition fiber tractography and diffusion tensor imaging. Improved understanding of these effects will allow clinicians to maximize the effectiveness of their treatments while minimizing toxicities.

Conclusion

Melanoma is a unique disease in that brain metastases are often the first manifestation of metastatic disease [4]. Large studies have failed to emphasize the epidemiological importance of melanoma [23]. Our study is the first to demonstrate that a SRS-only approach may avoid WBRT-associated leukoencephalopathy in a population exclusively comprised of melanoma patients. This finding is particularly significant because our study utilized a population of patients that had far less traditional chemotherapy than in previous investigations. Future directions for investigation include detailed assessments of neurocognitive functioning, quality-of-life, and correlation with

anatomic findings on other imaging modalities. In an era where targeted therapies like monoclonal antibodies and small molecule selective enzyme inhibitors are prolonging patient lives, a paradigm shift to SRS with its targeted approach and high effectiveness should be emphasized.

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