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CLINICAL STUDY

White matter changes in breast cancer brain metastases patients who undergo radiosurgery alone compared to whole brain radiation therapy plus radiosurgery

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Abstract Delayed toxicity after whole brain radiation therapy (WBRT) is of increasing concern in patients who survive more than one year with brain metastases from breast cancer. Radiation-related white matter toxicity is detected by magnetic resonance imaging (MRI) and has been correlated with neurocognitive dysfunction. This study assessed the risk of developing white matter changes (WMC) in breast cancer patients who underwent either WBRT plus stereotactic radiosurgery (SRS) or SRS alone. We retrospectively compared 35 patients with breast cancer brain metastases who received WBRT and SRS to 30 patients who only received SRS. All patients had evaluable imaging at a median of one year after their initial management. The development of white matter T2 prolongation as detected by T2 or FLAIR imaging was graded: grade 1 = little or no white matter T2 hyperintensity; grade 2 = limited periventricular hyperintensity; and grade 3 = diffuse white matter hyperintensity. After WBRT plus SRS, patients demonstrated a significantly higher incidence of WMC ($p < 0.0001$). After one year, 71.5 % of patients whose treatment included WBRT demonstrated WMC (42.9 % grade 2; 28.6 % grade 3). Only one patient receiving only SRS developed WMC. In long-term survivors of breast cancer, the risk of WMC was significantly reduced when SRS alone was used for management. Further prospective studies are necessary to determine how these findings correlate with neurocognitive toxicity. WBRT usage as initial management of limited brain disease should be replaced by SRS alone to reduce the risk of delayed white matter toxicity.

Keywords Brain metastasis · Gamma Knife · Stereotactic radiosurgery · Breast cancer · Leukoencephalopathy

Introduction

Whole brain radiation therapy (WBRT) has been used as a primary therapy for metastatic brain cancer for decades. Since the development of stereotactic radiosurgery (SRS), mounting evidence has questioned the up-front administration of WBRT in patients with newly diagnosed brain disease. In three randomized controlled trials, WBRT was no better than observation at improving overall survival or functional independence when combined with surgical resection or stereotactic radiosurgery (SRS) for limited disease [1–3].

Because of better targeted systemic disease options, an increasing number of patients have prolonged survivals despite the spread of cancer to the brain [4–6]. The standard administration of WBRT in the face of newly diagnosed brain metastases may not be an appropriate reflex reaction. WBRT leads to delayed brain white matter injury because of its direct effect on the cerebrovasculature and the oligodendroglia. As a result both demyelination and injury to the periventricular stem cell population effectively inhibits any neurogenesis repair mechanism [7–10]. Diffuse abnormalities of the white matter have been associated with neurocognitive decline in dementia,

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alcoholism, and multiple sclerosis [11–13]. Following WBRT, progressive and diffuse white matter changes (WMC) have been detected via magnetic resonance imaging (MRI) [14–16]. In as few as four months, patients in a randomized controlled trial with one to three brain metastases demonstrated significant neurocognitive toxicity after receiving WBRT and SRS versus SRS alone [17].

We recently evaluated the incidence of WMC in long-term survivors from lung cancer who had received either WBRT and SRS or SRS alone for the treatment of their brain metastases [18]. Using a simplified grading scale for white matter changes, we observed that the risk of these changes was significantly lower in patients who did not undergo WBRT. Because long-term survival with breast cancers is greater and more frequent than for lung cancers, we sought to evaluate the occurrence of WMC in a patient population more likely to be impacted by the delayed toxicities of treatment.

The present retrospective study was designed to evaluate the risk of developing WMC one year after patients with metastatic breast cancer received either WBRT plus SRS or SRS alone.

Methods

Patient population

Following Institutional Review Board approval, we retrospectively reviewed data from 264 consecutive patients who underwent Gamma Knife SRS for breast cancer brain metastases from 2001 to 2009. The Leksell Gamma knife units B, C, 4C, or Perfexion models were used during this interval. We identified 65 patients who survived at least one year after their initial treatment and who had MRI scans that could be evaluated for white matter changes. Thirty-five patients underwent both WBRT and SRS, while 30 patients underwent only SRS. We evaluated differences in these patients in age, sex, treatment with chemotherapy, number of SRS procedures, and number of tumors treated. We estimated the Breast-Graded Prognostic Assessment (GPA) score for each patient at or near the time of initial SRS [19].

WBRT and SRS

WBRT was administered at facilities closest to a patient's home. Prior to SRS, detailed records from these facilities regarding the WBRT treatment were obtained. The median total dose for the cohort was 33.75 Gy (range = 16–50.4 Gy) administered over a median of 14 fractions (range = 8–42). Some of the more protracted, lower-dose per fraction schedules used in these patients are often used in an attempt to limit toxicity. No patients underwent a second course of WBRT during the evaluation period. The completion date of the WBRT treatment was the time from which imaging follow-up was determined. In the cohort that received WBRT, the initial SRS procedure was considered 'boost' or 'early consolidation' treatment in 26 patients and 'late' salvage in four for new or recurrent tumors. Five patients had upfront SRS followed by WBRT at a subsequent time. For patients in the SRS only cohort, imaging follow up was calculated from the date of the first Gamma Knife procedure. All patients in the study underwent at least one SRS procedure. Ten of the patient who received WBRT only underwent a single SRS procedure, 12 had two SRS procedures, and the remaining 13 had three or more. In patients who had only SRS, five had a single procedure, 16 had two procedures, and nine had three or more. The details of our radiosurgical technique have been previously reported [20]. For the entire study population the median marginal radiosurgical dose was 18 Gy (range 10–20 Gy), while the median treatment volume was 5.0 cm^3 (range 0.1–51.3 cm^3).

Imaging evaluation

Following treatment, patients were instructed to obtain brain MRI imaging at three months intervals. Close clinical and radiological follow up are required for all patients with brain metastases in order to surveil them for new or recurrent tumors. MRI images from the time of initial treatment and at a median of one year after treatment were evaluated. The one year time point was selected on the basis of previously published literature evaluating the effects of WBRT on the white matter in long-term survivors of brain metastases demonstrating that meaningful white matter toxicity is detectable at this time [14–16]. We previously reported on a simplified qualitative grading scale for the evaluation of WMC that could be utilized in everyday clinical practice [18]. Briefly, T2 or FLAIR sequence images were scrutinized by two authors (T. S. and E. M.) who were blinded to the management paradigm and not originally involved in the patients' care. The white matter was graded according to the centrifugal pattern of radiation-induced white matter T2 prolongation [21]: grade 1 = little or no white matter hyperintensity; grade 2 = white matter hyperintensity limited to the periventricular region; and grade 3 = diffuse hyperintensity. Figure 1 depicts MRI images representative of each grade. Prior qualitative scales possessed numerous grades or involved many anatomic locations [14, 21, 22]. There are quantitative analyses that can be performed and these are more sensitive, but they require complex image processing on uniform images using expensive proprietary software [15].

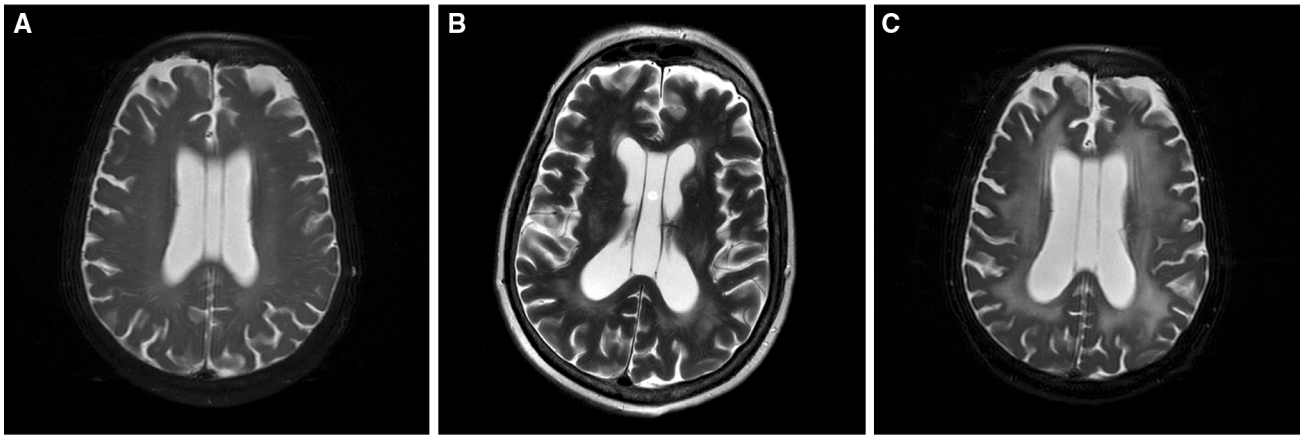

Fig. 1 T2-weighted axial magnetic resonance images representative of **a** grade 1, **b** grade 2, and **c** grade 3 white matter changes

Statistical analyses

Descriptive statistics like mean with standard deviation and median with range were utilized for continuous data. Categorical data were reported by frequencies and proportions. Variables pertaining to the two groups were compared with appropriate statistical tests to identify significant differences (SAS version 9.3, SAS Institute, Cary, North Carolina).

Normally distributed data were examined via the student's *t* test, while the Wilcoxon-Rank-Sum Test was used for non-parametric continuous data not meeting the normality assumption. Pearson's Chi Square test and Spearman's rank-order correlation were used for categorical data and Fisher's Exact Test was used for categorical data when the cells had an expected count of less than five.

Kaplan–Meier plots for grade 2 and 3 WMC free survival from the dates of initial intervention (SRS or WBRT) were constructed. Univariate analysis was performed using log rank statistics with $p < 0.05$ set as significant. Variables that were considered included SRS alone and WBRT plus SRS. Standard statistical processing software (SPSS, version 15.0 and Prism, version 4.0) was used.

Results

Patient characteristics

The patient cohorts receiving each treatment were similar (Table 1). No differences were noted in the rate of chemotherapy treatment between the two groups. While the number of tumors treated at the initial SRS procedures was significantly greater in the cohort receiving WBRT and SRS (4 vs. 2, $p < 0.008$), the total number of SRS procedures and total number of tumors treated by SRS were not significantly different. Marginal SRS tumor doses were significantly lower in the group receiving WBRT plus SRS versus the SRS-only group (medians of 17 Gy and 20 Gy, respectively, $p < 0.001$). This is representative of our

Table 1 Baseline characteristics of the study cohorts

	WBRT + SRS	SRS only	*p*-value
Total n = 65	n = 35	n = 30	
Age mean (SD)	51.3 (11.6)	54.6 (11.3)	0.25[a]
Chemotherapy	35 (100 %)	30 (100 %)	
Breast-graded prognostic assessment median (range)	2.5 (1–4)	2.75 (1.5–4)	0.21[b]
#SRS treatments median (range)	2 (1–10)	2 (1–6)	0.94[b]
#Total mets treated by SRS median (range)	7 (1–50)	4 (1–54)	0.10[b]
#Mets treated at initial SRS median (range)	4 (1–14)	2 (1–8)	0.008[b]
Marginal SRS dose, Gy median (range)	17 (10–20)	20 (11–20)	< 0.001[b]
Proximity of baseline MRI to initial treatment (months) median (range)	0.2 (−2.6–7)	−0.2 (−3.2–36)	0.90[b]
Time to graded imaging (months) median (range)	13.1 (8.4–19.8)	12.8 (8.7–39.1)	0.51[b]
Survival (months) median (range)	29.7 (11.0–115.5)	40.8 (12.3–154.4)	0.13[b]

[a] Based on student t-test

[b] Based on Wilcoxon rank-sum test

routine practice of lowering the SRS prescription dose in patients having received previous radiation therapy in order to balance tumor control and adverse radiation effects. Despite both groups harboring similar numbers of tumors, there was improved median survival in the SRS only group, although this did not achieve statistical significance (29.7 vs. 40.8 months; $p = 0.13$). The estimated breast cancer specific GPA scores for the two cohorts were not significantly different ($p = 0.21$). There was also no significant difference in estimated Karnofsky performance scores between the two cohorts at the one year evaluation ($p = 0.09$).

Imaging findings

The white matter grades were similar between the two treatment groups at the time of initial treatment, with 97.1 and 96.7 % of patients in the two cohorts not possessing any evidence of WMC at baseline (Table 2). Only one patient in each group had evidence of WMC at the time of initial management and this was only grade 2. After a median of 13 months, a significantly larger proportion of patients who received WBRT plus SRS demonstrated WMC versus those who had only SRS (71.5 % vs. 6.7 %, respectively; $p < 0.0001$). Of the patients demonstrating WMC in the WBRT plus SRS group, 28.6 % already demonstrated grade 3 abnormalities after a median of 13 months (Figs. 2, 3a, b). In the group treated with only SRS, a single patient showed a change in the white matter (3.3 %). No patients receiving only SRS for the treatment of their brain metastases developed grade 3 changes ($p < 0.0001$; Figs. 2, 3c, d). The 6, 9, 12 and 15 month rates of grade 2 WMC in patients who received WBRT plus SRS were 25.7, 31.4, 50.1 and 69.5 %, respectively. For the SRS alone cohort, these rates were 3.4, 3.4, 3.4, and 6.8 %, respectively (Fig. 4). Following WBRT plus SRS, the 6, 9, 12 and 15-month rates of grade 3 WMC were 5.7, 14.3, 14.3, and 28.0 %, while in the SRS alone cohort they were 0 % at four time points (Fig. 5). We evaluated whether the observed WMC in the WBRT-treated cohort were correlated with any particular total WBRT dose. There was no significant correlation ($p = 0.62$).

Table 2 White matter changes following treatment for brain metastases

	WBRT + SRS	SRS only	*p*
White matter score at baseline			
1	34 (97.1 %)	29 (96.7 %)	
2	1 (2.9 %)	1 (3.3 %)	
3	0	0	1[a]
White matter score at median 1 year imaging			
1	10 (28.6 %)	28 (93.3 %)	
2	15 (42.9 %)	2 (6.7 %)	
3	10 (28.6 %)	0	< 0.0001[b]

[a] Based on Fischer exact test

[b] Based on Pearson Chi square test

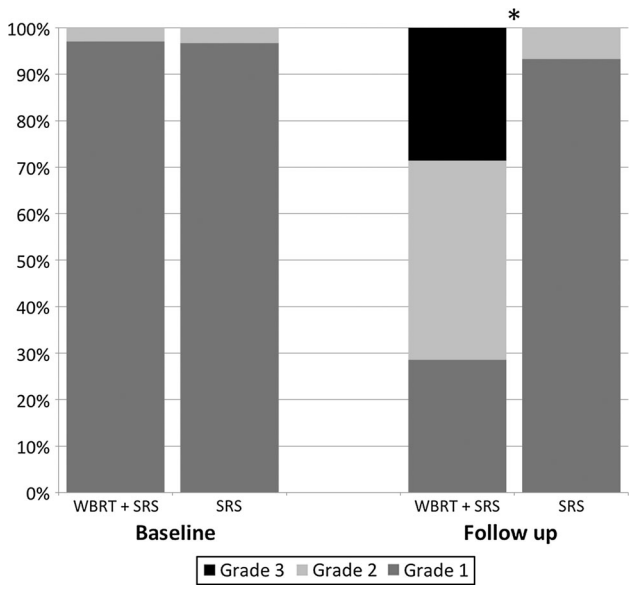

Fig. 2 Graph depicts changes in white matter grades between patients treated by whole brain radiation therapy (WBRT) plus stereotactic radiosurgery (SRS) and those treated only with SRS, as a percentage of the total number of surviving patients (*$p < 0.0001$)

Discussion

Prior to the development of more effective personalized and targeted therapies for patients with metastatic breast cancer, WBRT became the standard of care management. Since the median survival for patients with metastatic breast cancer to brain historically averaged four months [23, 24], a fatalistic view developed about this often end of life issue. Despite limited statistical effectiveness, administration of WBRT became a reflexive strategy widely employed, in part, because of the limited planning needed and its ease of administration. Numerous attempts to modify WBRT via different fractionation schedules or the use of radiation sensitizers failed to improve its efficacy [25–28]. To improve the safety profile of WBRT, radioprotectants like memantine are being explored. A prospective, randomized, double-blind, placebo controlled trial of memantine to prevent WBRT-related cognitive dysfunction failed to significantly show efficacy in preserving delayed recall, a primary endpoint of the study, although there was a small but significant delay in time to cognitive failure and some improvement in specific executive domains [29]. Cognitive function after combining

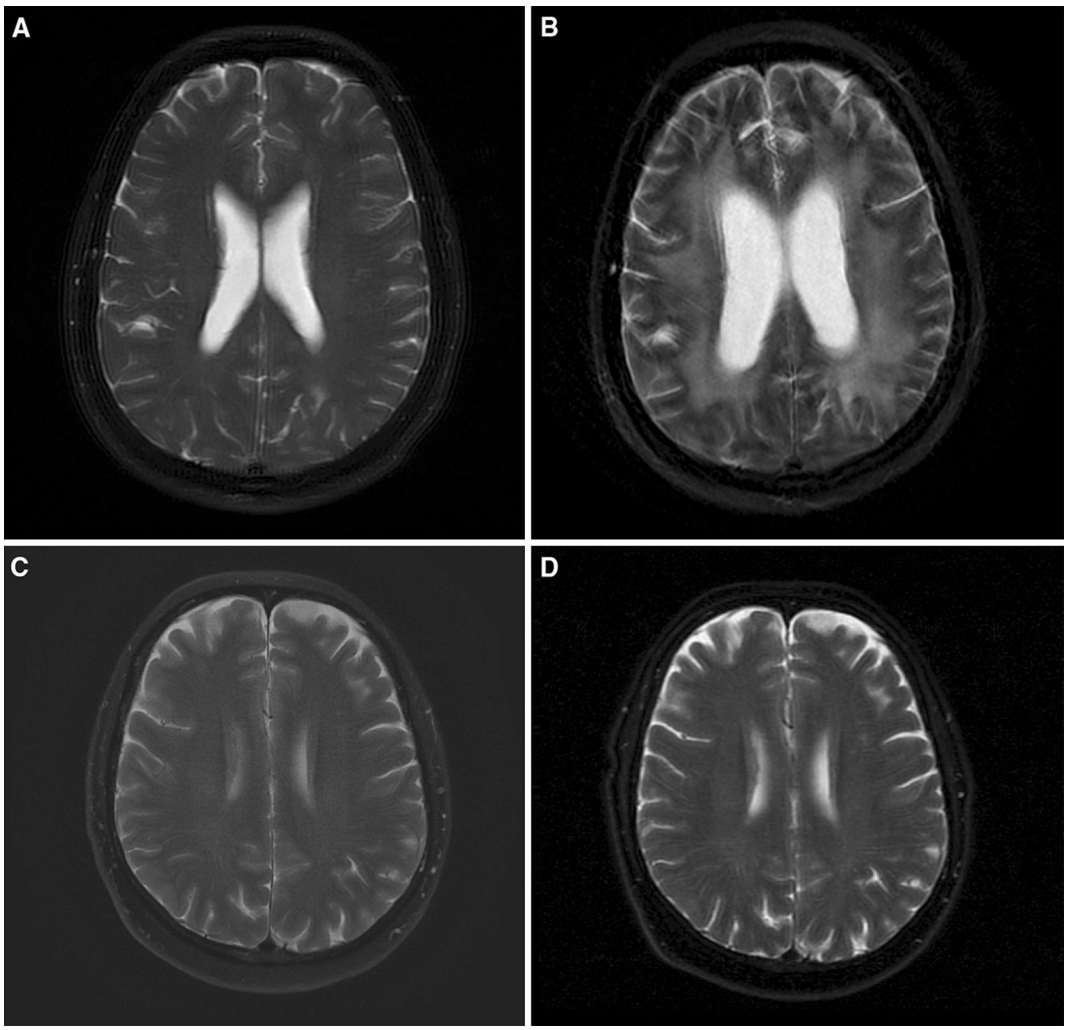

Fig. 3 T2-weighted magnetic resonance images demonstrate a patient at **a** baseline and at **b** one-year imaging follow up after whole brain radiation therapy and stereotactic radiosurgery, compared with images from a patient at **c** baseline and at **d** one-year follow up after only stereotactic radiosurgical therapy

memantine with WBRT has not been directly compared to an SRS only paradigm.

With the advent of better systemic therapies, longer term survival after the discovery of brain metastases has become possible. One year survival of patients harboring brain metastases between 2005 and 2009 was 34 %, whereas patients treated between 1983 and 1989 only made it to one year 15 % of the time [30]. In a series of 675 patients who received SRS for brain metastases, 6.5 % survived past four years [5]. Five year survivals range from 4.2 to 7.8 % [4, 6]. Improved life-expectancy, the failure of WBRT to improve survival when added to focal therapies [1–3], and concerns over the toxicity of WBRT [17, 31, 32] have even led clinicians to evaluate other options for brain disease.

Changes to the brain's white matter following WBRT have been increasingly detected [2, 14–16, 33–35]. Progressive WMC correlates with increasing neurocognitive dysfunction [11–13]. SRS has evolved as an important treatment for brain metastases and has several advantages over other strategies [36–40]. It is usually performed as a single surgical procedure. As a non-invasive alternative to craniotomy for solitary brain metastases and a preferred option for patients with multiple brain metastases, SRS targets each individual tumor with both highly conformal dose delivery and rapid dose fall off outside the target (selectivity). Each treated tumor receives a higher actual dose that greatly increases the radiobiological response. If additional tumors are detected in the future, it can be repeated with a similar low risk profile [2]. Because the tumor controlling dose is limited to one or more small volumes, SRS limits diffuse adverse radiation effects to the surrounding white matter. Chang et al. reported that an SRS only paradigm for brain metastases management can prevent the neurocognitive dysfunction associated with WBRT [17]. Tooze et al. performed neurocognitive testing on patients whose pituitary tumors were treated by SRS

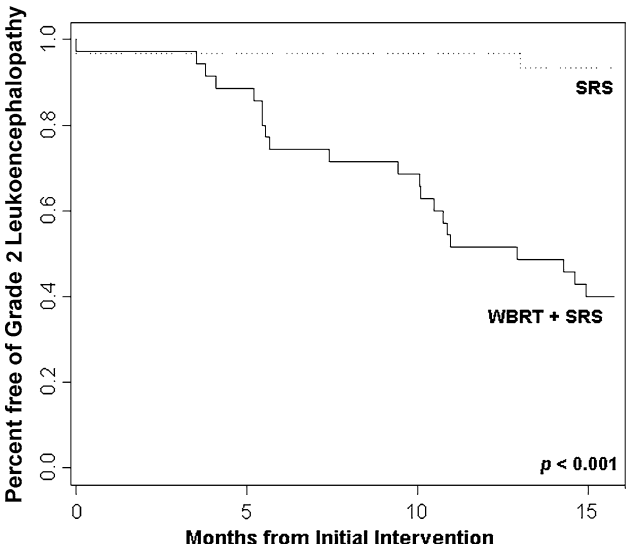

Fig. 4 Kaplan–Meier *curve* of the development of grade 2 white matter changes after WBRT plus SRS (*solid line*) versus SRS alone (*dashed line*). Patients who underwent only SRS demonstrated a significantly reduced rate of grade 2 white matter changes

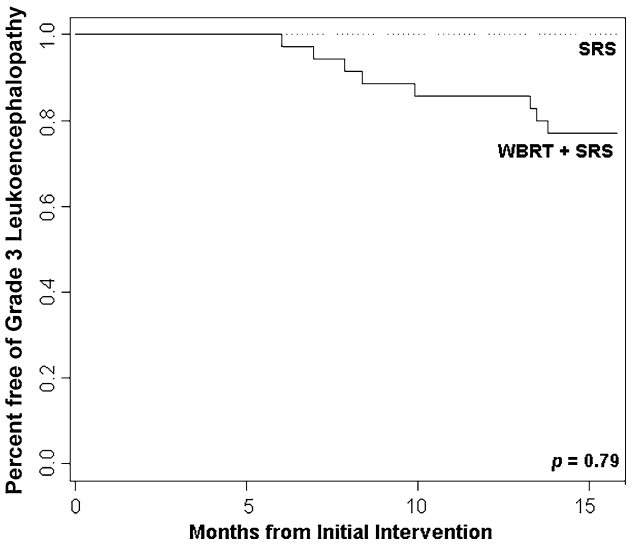

Fig. 5 Kaplan–Meier *curve* of the development of grade 3 white matter changes after WBRT plus SRS (*solid line*) versus SRS alone (*dashed line*). Although patients who underwent SRS alone did not demonstrate any grade 3 white matter changes, the difference did not achieve statistical significance

and found no evidence to suggest that SRS impairs neurocognitive functioning [41]. We previously reported a reduced risk of WMC development in lung cancer patients who underwent SRS alone compared to patients who underwent WBRT and SRS [18]. In that report we found that almost 90 % of patients treated with WBRT plus SRS developed WMC after a median of one year, whereas only one patient treated with SRS alone developed MRI-defined WMC. Almost half (46 %) the lung cancer cohort manifested grade 3 changes at one year. When patients survived two years, all but one patient exposed to WBRT demonstrated WMC.

Breast cancer is the second leading cause of cancer death in women and up to 20 % of patients will develop brain metastases [42]. With advanced treatment options more widely applied, breast cancer patients have an improved prognosis and longer survivals [43]. SRS patients in our experience with breast cancer had longer median survivals (40.8 months) than did lung cancer patients (28.2 month) [18]. Improved survivals may in part be related to targeted therapies available to breast cancer patients with certain receptor profiles [43]. The ability to reduce delayed therapeutic toxicity may be even more relevant to breast cancer patients. In the clinic we note that such patients do not report the functional impairments of short term memory loss and executive function disabilities previously seen in WBRT patients [44]. Chemotherapy has been implicated as an etiology for white matter changes but the two cohorts were not significantly different in their exposure to chemotherapy [45]. Tumor burden has been implicated in neurocognitive decline in patients with brain metastases, but the overall disease burden between the cohorts was not different [46, 47]. The present results support our previous finding that avoidance of WBRT appears to diminish the likelihood of WMC in patients with brain metastases. Of interest in this series, we found that the development of WMC occurred in nearly 20 % fewer breast cancer patients compared to non-small cell lung cancer patients. It was also less severe (grade 3 of 28.6 % vs. 46 %, respectively). Among the possible reasons for this might be the generally younger age of patients in the breast cohort (by almost 10 years). Ebi et al. observed that older age was a significant risk factor for the development of WMC after WBRT [16]. It could also be related to the differences in systemic therapies or to the fact that the breast cancer patients were all female. Neurotoxicity and cognitive dysfunction from other causes can demonstrate gender differences [48, 49].

The present study is limited by its retrospective design and of the absence of formal neurocognitive and quality-of-life assessments. Like our previous study, it serves as a potential stimulus to develop multi-centered prospective randomized trials. Such a trial was opened in 2013 under the sponsorship of the North American Gamma Knife Consortium. This prospective randomized trial will use primary endpoints of neurocognitive and quality-of-life assessments in comparing patients who undergo WBRT plus SRS compared to patients who undergo SRS alone. Although qualitative assessments of white matter changes are not as precise and accurate as quantitative ones, they offer the benefit of rapid and easy use, and thus can be incorporated into daily practice. A quantitative comparison

of brain volume changes utilizing a similar study design is planned. Identifying the dominant etiology of neurocognitive dysfunction in patients with brain metastases is problematic since poor brain tumor control has also been linked to neurocognitive dysfunction. Increasing data indicate that the metastatic tumor volume rather than the number of brain metastases is more important to patient survival [50]. Rather than WBRT, in the future initial SRS followed by repeat salvage SRS may likely be a preferred paradigm. Tumor control and preservation of neurological function represent the twin goals of current management of patients with metastases to the brain. Selecting the most appropriate treatment course for patients with the diagnosis of metastatic brain cancer must be individualized to provide the maximum benefit while limiting potential long term toxicities.

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