

Clinical Study

Safety of multiple stereotactic radiosurgery treatments for multiple brain lesions

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Summary

Background: Stereotactic radiosurgery (SRS) is a widely used therapy for multiple brain lesions, and studies have clearly established the safety and efficacy of single-dose SRS. However, as patient survival has increased, the recurrence of tumors and the development of metastases to new sites within the brain have made it desirable to repeat treatments over time. The cumulative toxicity of multi-isocenter, multiple treatments has not been well defined. We have retrospectively studied 10 patients who received multiple SRS treatments for multiple brain lesions to assess the cumulative toxicity of these treatments.

Methods: In a retrospective review of all patients treated with SRS using the X-knife (Radionics, Burlington, MA) at Westchester Medical Center/New York Medical College between December 1995 and December 2000, 10 patients were identified who received at least two treatments to at least 3 isocenters and had a minimum follow-up period of 6 months. Image fusion technique was used to determine cumulative doses to targeted lesions, whole brain and critical brain structures. Toxicities and complications were identified by chart and radiological review.

Results: The average of the maximum doses (cGy) to a point within the whole brain was 2402 (range 1617–3953); to the brainstem, 1059 (range 48–4126); to the right optic nerve, 223 (range 14–1012); to the left optic nerve, 159 (range 17–475); and to the optic chiasm, 219 (range 15–909). There were no focal neurological toxicities, including visual disturbances, cranial nerve palsies, or ataxia in any of the 10 patients. There were also no global toxicities, including cognitive decline or secondary tumors. Only one patient developed seizures that were difficult to control in association with radiation necrosis.

Conclusions: Multiple SRS treatments at the cumulative doses used in our study are a safe therapy for patients with multiple brain lesions.

Introduction

Stereotactic radiosurgery (SRS) is now a widely used and accepted treatment modality for a number of intracranial diseases. Cerebral metastases are ideally suited for treatment with SRS because they are frequently spherical in shape with radiographically distinct margins and are commonly at the gray–white junction, where toxicity to critical structures is minimal [1]. Previous studies have demonstrated the response of metastases to SRS [2–6]. For some patients, treatment with SRS may be as beneficial as open surgery [7–9]. SRS can be applied to any site in the brain, avoids a craniotomy, and is cost effective [10]. SRS

is particularly attractive as a non-invasive treatment option in cases of multiple brain lesions.

Approximately 1.4 million new cases of invasive cancer are diagnosed every year in the United States [11]. Of these, up to 50% will develop cerebral metastases [12]. Over the last two decades, advances in early diagnosis and improved treatment protocols have resulted in a significant increase in the survival of patients with systemic cancers. Despite these advances in solid tumor management, treatments for cerebral metastases remain limited, with resulting neurological impairment that impacts significantly on quality of life during the survival period. The safety and efficacy of single-dose SRS treatments has been well established

[13–15]. However, as more treated patients survive for longer periods, some develop recurrence of tumors and metastases to new sites within the brain, necessitating additional courses of SRS [16,17]. Deleterious effects of whole brain radiation therapy (WBRT) such as neuropathy, dementia, and other irreversible neurotoxicities have become evident in patients who survive longer [18,19]. The cumulative long-term effects of multiple SRS treatments have not been fully established [20,21]. In this study, we reviewed a series of patients who received multiple, multi-isocenter treatments to determine the maximum cumulative dose to cerebral cortex and critical brain structures, and to assess toxicities and complications for the volumes irradiated.

Methods

Patient population

A retrospective review was conducted of all patients treated with SRS between December 1995 and December 2000 at Westchester Medical Center/New York Medical College (Valhalla, NY). Those who had at least 2 SRS treatments to at least 3 isocenters and had a minimum follow-up period of 6 months were included in the study. Of the 231 patients treated with SRS during this period, 10 patients met protocol criteria.

Cumulative dose calculations

X-knife image fusion software (Radionics, Burlington, MA) was used to fuse all treatment images and data to a reference CT image (initial CT before first SRS treatment). Cumulative and individual doses to each lesion, the whole brain, the optic chiasm, and the right and left optic nerves were determined for each patient with the X-knife planning software. Starting with the first treatment data, the collimators and beams at each target for the subsequent treatments were entered in the software according to the treatment history. The calculations produced dose–volume histograms for comparison of composite and individual plans. The cumulative average doses (total dose/tissue volume), high 10% doses (highest dose delivered to 10% of the tissue volume), and maximum doses for whole brain and critical brain structures were calculated for each patient. These cumulative doses were then averaged for the 10 patients treated.

Outcome measures

Both MRI and CT imaging studies were obtained for all 10 patients. Demographic data, diagnosis, adjuvant treatments, length of survival, and complications were obtained for all the patients through a review of charts in the neurosurgery office as well as in the office of radiation medicine. Toxicities were analyzed in relationship to treatment parameters. We looked for signs and symptoms of global toxicities (NCI grading 0–4) and focal neurologic deficits [22].

Results

Demographics

Ten patients (9F, 1M) between the ages of 28–75 years (mean 47 years) were included in the study. The follow-up period ranged from 6 to 39 months (mean 14.6 months). Eight of the 10 patients in this study were being treated for metastases (breast, 4; lung, 4). One patient had a multicentric astrocytoma, and one had a pituitary adenoma with bilateral invasion of the cavernous sinus. Five patients had craniotomy for resection of tumor before treatment with SRS, while 9 were treated with WBRT at doses of 2500–3000 cGy.

Dose to target lesions

Each patient underwent at least two treatments to at least 3 isocenters with a mean of 5.7 isocenters treated (range 3–8) (Table 1). Individual treatment doses used an average collimator size of 2.44 cm (range 1.67–4.0) and an average maximum collimator size of 3.7 cm (range 2.5–5.0) (Tables 1 and 2) indicating that significant volumes were treated. The mean dose delivered was 1653 cGy (range 567–2166), with a mean maximum dose of 1829 (range 625–2240) on the basis of the Radiation Therapy Oncology Group recommended doses using isodose diameter criteria [22]. The total interval between the first and last treatment ranged from 4 to 39 months (mean 14.6 months).

Dose to critical structures

Despite multiple treatments to tumors throughout the cranium, maximum doses to critical structures remained remarkably small, ranging from a mean of 159 to the left optic nerve to 1059 to the brain stem

Table 1. Multiple, multi-isocenter treatment parameters

Patients*	Number of treatments	Number of isocenters	Collimator size (cm)		Prescribed dose (cGy)		Treatment period (months)
			Average	Maximum	Average**	Maximum***	
A	4	5	2.75	3.5	1550	2120	39
B	2	8	2.0	5.0	1926	2000	12
C	3	4	1.94	3.0	2166	2240	6
D	2	8	2.65	5.0	1912	2100	7
E	2	8	1.9	3.0	1854	2000	13
F	2	3	4.0	5.0	1200	1200	4
G	2	3	3.1	4.0	567	625	6
H	3	5	2.53	3.0	1850	2000	39
I	2	6	1.67	2.5	1861	2000	7
J	2	7	1.89	3.0	1643	2000	11
Average	2.4	5.7	2.44	3.7	1653	1829	14.6

*Patients A, C, H, and J had metastatic lung carcinoma; patients B, D, E, and I had metastatic breast carcinoma; patient F had a multicentered astrocytoma; and patient G had a pituitary adenoma (the prescribed dose was much lower due to the size of the lesion and its closeness to the optic chiasm).

**Average = averaged over all treatments.

***Maximum = highest dose in a single treatment.

Table 2. Cumulative whole brain dose, collimator size, and percent dose

Patients	Average target dose (cGy)	Average collimator size (cm)	Whole brain dose (cGy)	Whole brain dose/average target dose $\times 100$ (% dose)
A	1550	2.75	443	28.5
B	1926	2.0	401	20.8
C	2166	1.94	216	10.0
D	1912	2.65	476	24.9
E	1854	1.9	320	17.3
F	1200	4.0	362	30.2
G	567	3.1	136	24.0
H	1850	2.53	89	4.8
I	1861	1.67	203	10.9
J	1643	1.89	192	11.7
Average	1653	2.44	284	18.31

(Table 3). No focal toxicities were associated with any of the cumulative doses received. No patients complained of or were found to suffer from a new visual field cut, hemiparesis, ataxia, or cranial nerve deficit.

Grade 4 toxicity

The average of the maximum doses to a point within the whole brain (excluding the planned treatment volume) was 2402 cGy (range 1617–3953) in addition to the 3000 cGy WBRT given to most of the patients before

SRS treatments. The mean whole brain/average target dose ratio (Table 2) was only 18.31%, again demonstrating that even multiple treatments of multiple metastases can focus most of the dose on the tumors and spare most normal cerebrum. Higher ratios were related more to collimator size than to the absolute number of lesions or treatments. The larger the collimator size, the higher the whole brain to average target dose ratio. Only one patient developed difficult-to-control seizures secondary to radiation necrosis 2 years after WBRT and initial SRS treatment (see case study).

Case study: patient E

A 42-year-old white female with a history of Stage T2N0M0 breast carcinoma (treated with modified mastectomy and chemotherapy) presented 6½ years later with complaints of posterior headache and neck pain. At the time of diagnosis of cerebral metastasis, the patient had been receiving 2 years of high-dose chemotherapy for bone, liver, and lung metastases, and she continued to receive high-dose chemotherapy through the remainder of her life. The patient was neurologically well except for left-sided mild dysmetria and dysdiadochokinesia. MRI imaging revealed 4 metastatic brain lesions, the largest in the left cerebellum measuring 5 cm; and WBRT was begun (3000 cGy total, 250 cGy/fraction). A suboccipital craniotomy was performed for resection of the largest lesion, and

Table 3. Average, high 10%, and maximum total doses to critical structures averaged over 10 patients

Critical structure	Average dose (cGy)* (range)	High 10% (cGy)** (range)	Maximum dose (cGy)*** (range)
Chiasm	113 (115–401)	191 (15–831)	219 (15–909)
Right optic nerve	110 (13–357)	205 (13–914)	223 (14–1012)
Left optic nerve	77 (14–140)	152 (16–471)	159 (17–475)
Brain stem	328 (15–1503)	814 (24–3444)	1059 (48–4126)
Whole brain	284 (89–476)	1186 (460–2014)	2402 (1617–3953)

*Total dose/tissue volume.

**Highest dose delivered to 10% of the tissue volume.

***Maximum to a point within the whole brain or critical structure.

then the patient received SRS (dose 1800–2000 cGy) for the 3 remaining lesions and the tumor bed (Figure 1). The patient tolerated the treatments well and returned to work 3 months after SRS.

One year later the patient again developed headaches, this time with numbness of the hands and right temporal hemianopsia. MRI imaging revealed 3 new lesions and a small recurrence adjacent to the surgical site. The 4 lesions were treated with SRS (1335–2000 cGy) 15 months after the first SRS treatment (Figure 2). The patient again did well for another year when she developed focal seizures that were difficult to control in association with radiographic evidence of radiation necrosis in the left frontal–parietal region. A closely spaced new lesion in the left frontal–parietal region and an additional right parasagittal lesion resulted in this area receiving a significant dose from the second SRS treatment. The initial SRS dose to this region was 2000 cGy (1800 cGy to the 90% isodose surface, 2.75 cm collimator). The second dose was 1335 cGy (1200 cGy to the 90% isodose surface, 3.0 cm collimator) with an overlapping dose from the right parasagittal lesion that received 1900 cGy (1800 cGy to the 90% isodose surface, 1.5 cm collimator).

Discussion

The goal of SRS is disease control with fewer complications than result from alternative treatments. At many centers, multiple metastatic lesions are now aggressively treated with SRS primarily on the basis of its known efficacy in treating a small number of lesions [2,23–26]. Our results suggest that the impact of doses received in previous SRS treatments may be negligible on toxicity from future SRS treatments, even in patients who survive considerably longer than

the 1 year average [27]. Cortical damage in terms of cognitive decline was not observed in any patient, and symptomatic radiation necrosis was seen in only one lesion in one patient. Our techniques demonstrated that the cumulative doses to the whole brain and to critical structures were minimal unless several lesions presented sequentially and were immediately adjacent to a structure (Table 3). A previous study has also demonstrated that later treatments contribute little to the cumulative dose of previously treated lesions, although total dose can be influenced by lesions in closer geographic proximity to each other and with the increased number of lesions treated over time [28]. Other groups have also used similar treatment planning programs to optimize for multiple isocenters [29]. The techniques used in this study could easily be applied so that the total dose can be monitored continuously.

Traditionally, brain toxicity after radiation therapy has been analyzed with specific reference to treatment-related necrosis [23,30]. For many years, it was felt that fractionated radiation would result in greater disease control while sparing normal tissue. Studies over several decades of the toxicity and efficacy of standard radiation treatments have provided important concepts regarding tumor growth and normal tissue repair, specifically cell reassortment, repopulation, and reoxygenation, in addition to the determination of early *versus* late responding parenchyma and endothelial cell (vascular) damage [31]. However, toxicity related to SRS relates almost exclusively to volume and total dose [30]. Single-dose equivalent mathematical models, different from those used with fractionated treatments, can reliably predict the 1% and 3% risk of radiation necrosis based primarily on dose and volume [22,32,33]. However, exceptions to the predictive models include the optic apparatus, facial and trigeminal nerves, and brainstem. The biological equivalent

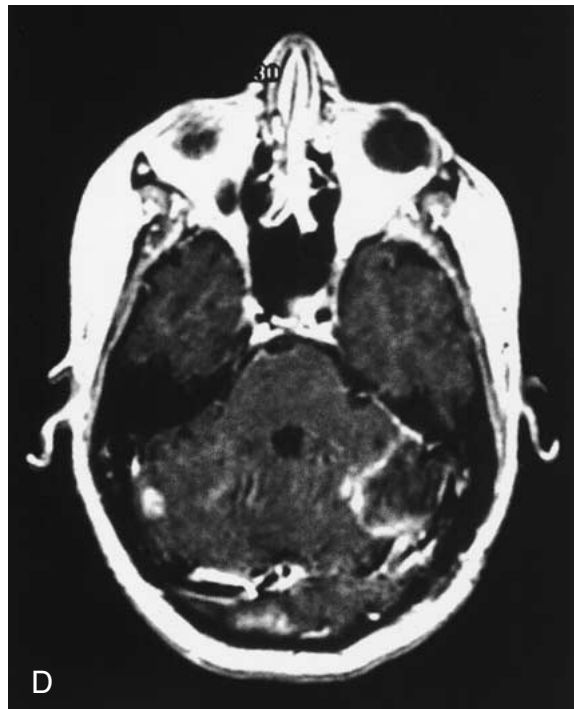
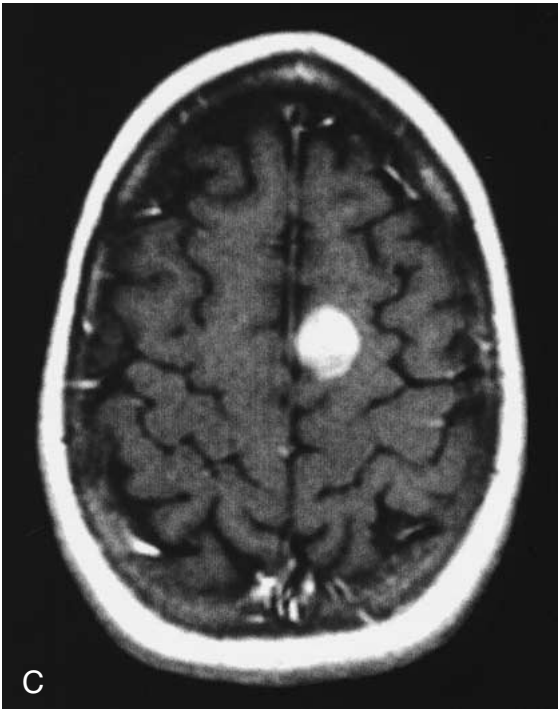
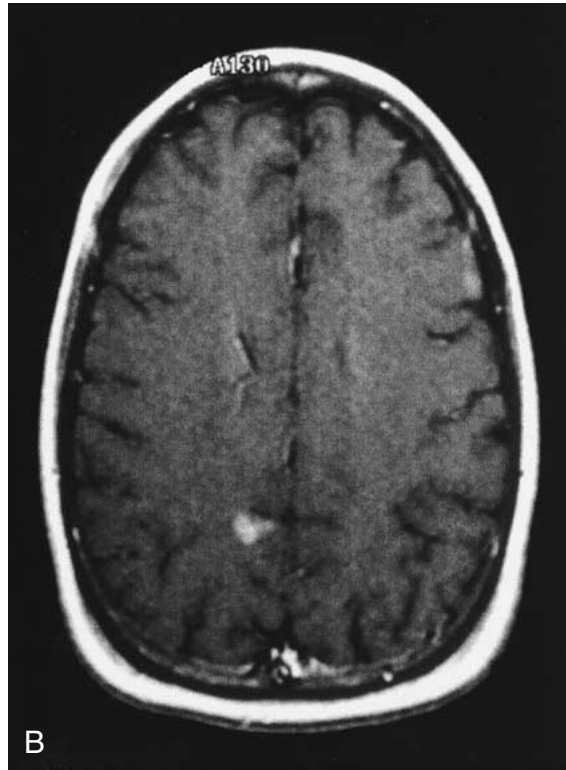
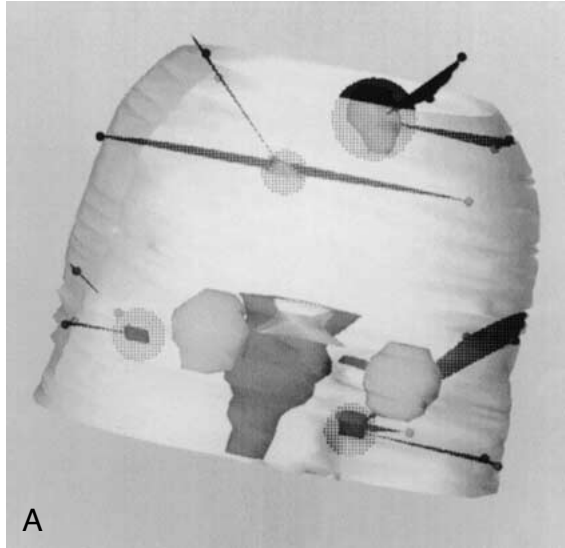


Figure 1. (A) 3D image of the SRS plan showing critical structures (optic nerves, globe, chiasm, and brainstem) and the 4 target sites (left cerebellar post-surgical tumor bed, right cerebellar, left posterior frontal, right parietal). (B) Axial MRI with gadolinium revealing small right parietal metastasis. (C) Axial MRI with gadolinium revealing left posterior frontal metastasis. (D) Axial MRI with gadolinium revealing right cerebellar metastasis and left cerebellar post-surgical tumor bed.

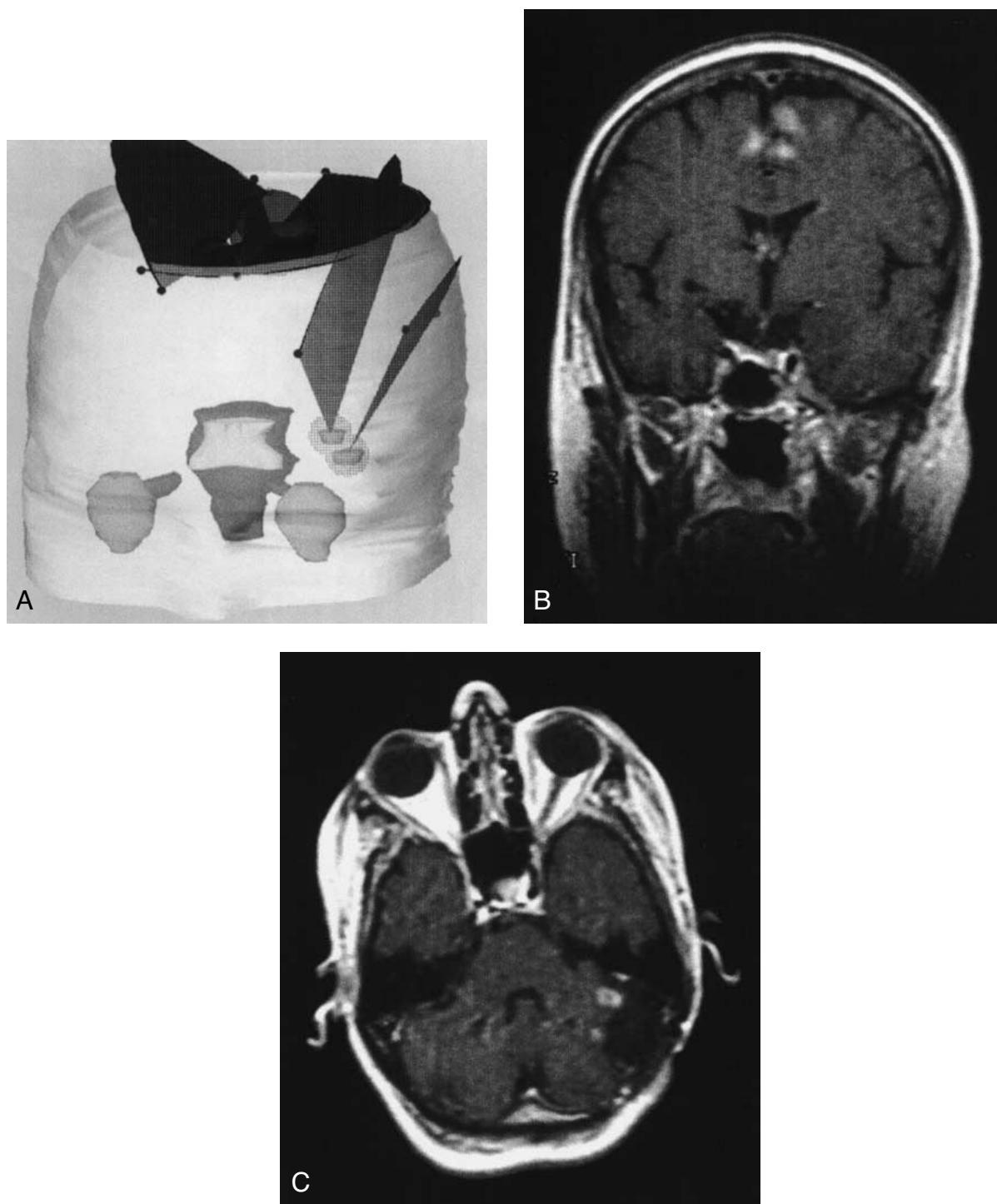


Figure 2. (A) 3D image of SRS plan showing critical structures and the 4 target sites (2 left cerebellar and 2 superior fronto-parietal). (B) Coronal MRI with gadolinium revealing left and right fronto-parietal metastases (lesions on the left were targeted as one site). (C) Axial MRI with gadolinium revealing 2 left cerebellar lesions adjacent to the operative site.

dose (BED) model still focuses on late tissue damage (necrosis) as an end point rather than clinical outcome from cumulative- and single-dose treatment.

Theoretically, both general and specific dose toxicities related to SRS could be significantly impacted by factors such as tumor volume, previous radiation, chemotherapy or surgery, vascular insufficiency, and partial volume dose. Nine of ten patients in this current study received WBRT and multiple courses of chemotherapy before SRS and still tolerated the total radiation doses received.

Conclusion

Multiple SRS treatments at the cumulative doses used in this study (whole brain, 2402 cGy (range 1617–3953); brainstem, 1059 cGy (range 48–4126); right optic nerve, 223 cGy (range 14–1012); left optic nerve, 159 cGy (range 17–475), and optic chiasm, 219 cGy (range 15–909)) are safe and effective in the management of patients with multiple brain lesions. Assessing the effects of cumulative doses with image fusion technology may become increasingly important with improved patient survival and the more common use of multiple treatments. With multimodality therapy the norm rather than the exception, all treatment-limiting factors that could affect outcome must be identified.

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