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Changes in regional cerebral blood flow in irradiated regions and normal brain after stereotactic radiosurgery

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Objective: To elucidate the radiation effect on the normal brain after stereotactic radiosurgery (SRS), we evaluated the change in regional cerebral blood flow (CBF) in targeted and extra-targeted areas according to the radiation dose given. ***Methods:*** Thirteen patients who underwent SRS for brain tumors or arteriovenous malformations were included in this study. Maximum radiation doses to the lesion ranged from 24 to 37 Gy. Mean and regional CBF were measured by ^{99m}Tc-HMPAO scintigraphy with graphic analysis, performed at before, 2 weeks and 3 months (5 patients) after SRS. Under the co-registration with the CT with superimposed isodose distribution, ROIs were set on target (37–20 Gy), peri-target (20–5 Gy) and out-of-field (5–2 Gy and less than 2 Gy) areas on the quantitative SPECT images. ***Results***: Significant reductions in mean CBF (by 7%) and regional CBF in the peri-target areas (by 5–7%) and out-of-field areas (by 6–22%) were recognized at 2 weeks and 3 months after SRS. Regional CBF in the target and peri-target areas did not significantly change, presumably because there was little or no normal tissue in these areas. ***Conclusion:*** These results suggest that subclinical regional CBF reduction occurs after SRS in the normal brain in out-of-field of radiation.

Key words: SPECT, ^{99m}Tc-HMPAO, stereotactic radiosurgery, regional cerebral blood flow

INTRODUCTION

STEREOTACTIC RADIOSURGERY (SRS), with a single large dose of irradiation in a well-collimated beam to a small treatment volume, has increased in popularity for the treatment of intracranial tumors as an alternative to surgical resection.[1,2] SRS allows for the delivery of a high dose of radiation to a tumor volume with rapid fall-off of the dose. The procedure is non-invasive and is much more feasible due to fewer anatomic constraints of tumor location,[3,4] but subclinical toxicity for the normal brain has not been sufficiently investigated. Although the primary effect of radiation on the central nervous system is considered to be caused by vascular damage,[5–7] little information is available regarding the effect on regional cerebral blood flow (CBF) in irradiated regions and surrounding normal tissue in correlation with the actual irradiation dose.

Technetium-99m hexamethylpropylene amine oxime (^{99m}Tc-HMPAO) is a widely used brain perfusion imaging agent that can measure regional CBF non-invasively, and the recent co-registration technique has enabled monitoring regional CBF in each radiation dose area obtained from isodose distribution on CT or MR imaging at planning.

This study was designed to investigate the radiation effect of SRS on brain tissue perfusion and to describe its relationship to the dose of radiation given.

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MATERIALS AND METHODS

Patients

Thirteen patients with 20 intracranial lesions were included in this study (age range 27–74 yr, mean 52 yr: 8 women, 5 men). The histopathologies and locations of lesions are listed in Tables 1 and 2. The mean maximum diameter of the lesions was 23 mm. All the patients underwent regional CBF measurement with ^{99m}Tc-HMPAO (Nihon Medi-Physics, Tokyo, Japan) before and 2 weeks after SRS. Of the 5 patients with benign lesions (2 arteriovenous malformations, one each of meningioma, hemangioblastoma and astrocytoma), 3 months' follow-up of regional CBF study was also available.

None of the patients had been treated for the brain lesions before or during the follow up period of the present radiosurgery. During the follow up period, no patient received chemotherapy and none of the lesions enlarged.

Stereotactic Radiosurgery

All the patients were treated with 10-MV photons in a linear accelerator (LINIAC ML-15MDX, Mitsubishi Electric, Japan) with a multi-arc method in which irradiation accuracy was estimated to be within ± 1 mm. Treatment planning was performed with contrast-enhanced CT and planning software (Marui Medical Inc., Tokyo, Japan). The SRS doses delivered to the margin of the legion ranged from 14 to 25 Gy (mean 23 Gy) and the maximum doses ranged from 24 to 37 Gy (mean 29 Gy).

Mean and Regional CBF Measurements

Mean and regional CBF measurement using ^{99m}Tc-HMPAO was performed by a Patlak plot and ROI method.[8] Before the SPECT study, radionuclide angiography was performed to calculate mean CBF. After the bolus injection of 370 MBq of ^{99m}Tc-HMPAO into an antecubital vein, data were acquired in a 128 × 128 format for 100 s at 1-s intervals with a rectangular gamma camera (Shimadzu 510R, Kyoto, Japan). Time activity curves of the aortic arch and brain were analyzed to obtain a brain perfusion index by a graphic approach. Mean CBF was calculated from the brain perfusion index by means of a linear regression equation. After additional intravenous injection of 370 MBq of ^{99m}Tc-HMPAO, SPECT imaging was carried out by means of a high-resolution SPECT system with three-headed rotating gamma cameras (Prism 3000, Marconi Medical Systems, Cleveland, OH). The acquisition of projection data was started at 10 minutes after injection and lasted 20 minutes. Data were accumulated for 30 angles (4 step, total 120 with 40 seconds per angle) for each detector. A ramp filter was used for image reconstruction in a 64 × 64 image matrix. The resolution was 9.37 mm full width at half maximum in the center of the reconstructed slice. These original SPECT images were then converted to quantitative SPECT images by applying of Lassen's correction algorithm.

Table 1 Histopathology of the lesions

Diagnosis	No. of patients	No. of lesions
Metastasis	6	13
AVM	3	3
Astrocytoma*	2	2
Hemangioblastoma	1	1
Meningioma	1	1

AVM, arteriovenous malformation
*Includes one each of WHO grade 2 and grade 3

Table 2 Locations of the lesions

Location	No. of lesions
Frontal lobe	5
Parietal lobe	3
Temporal lobe	2
Occipital lobe	5
Cerebellum	3
Cerebellopontine angle	1
Hypothalamus	1

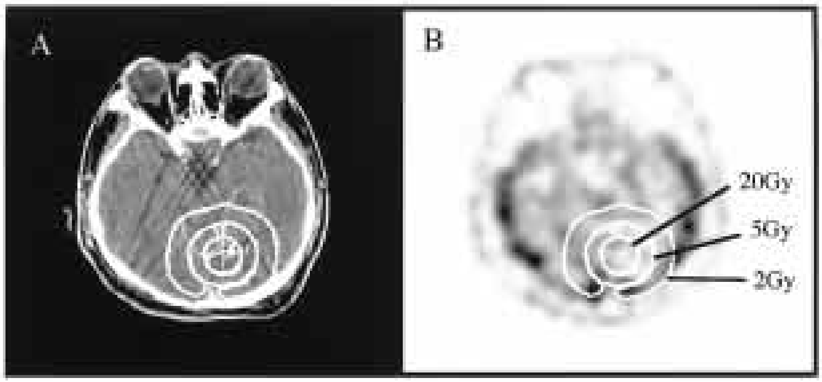

Fig. 1 ROI setting for lesion and surrounding area. Under the reference of each of 20 Gy, 5 Gy and 2 Gy isodose line on the CT image (A), circumscribed ROIs were manually placed over the 37–20 Gy, 20–5 Gy and 5–2 Gy dose area on the co-registered quantitative SPECT image (B).

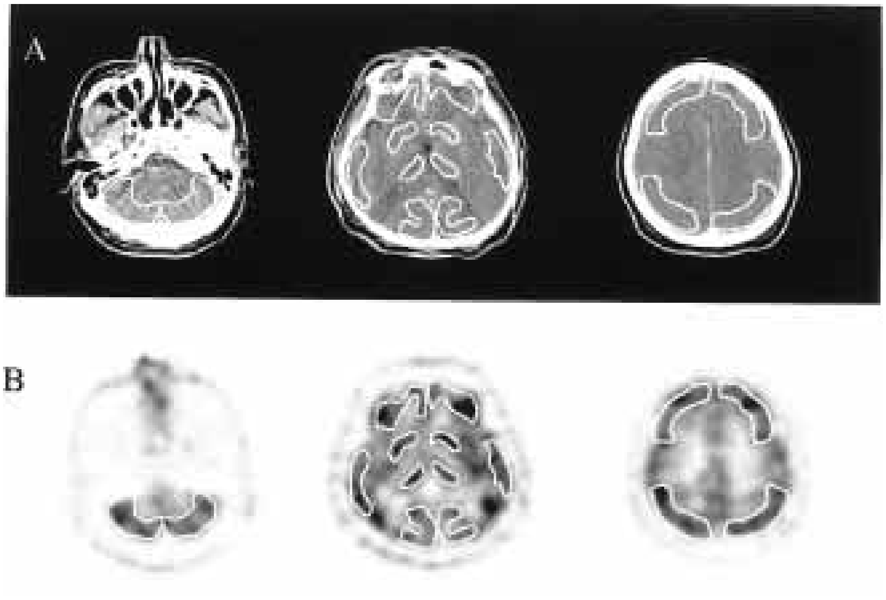

Fig. 2 ROI setting for the areas of less than 2 Gy dose given. Slices of CT (A) and corresponding quantitative SPECT image (B) outside the 2 Gy isodose line are shown with an overlay of a regional schema of each ROI.

Table 3 Changes of mean CBF

Mean CBF (m*l*/100 g/min)		
Prior to SRS (n = 13)	2 wks after SRS (n = 13)	3 mo after SRS (n = 5)
46.0 ± 6.2	42.7 ± 5.0* (–7)	43.0 ± 5.6* (–7)

Data are presented as mean ± SD
CBF, cerebral blood flow; SRS, stereotactic radiosurgery
Numbers in parentheses are mean percent changes to prior to SRS
n = number of patients
*statistically significant decrease to prior to SRS, $p < 0.05$

Table 4 Changes of regional CBF in 37–20 Gy, 20–5 Gy and 5–2 Gy dose level

ROI	Regional CBF (m*l*/100 g/min)		
	Prior to SRS (n = 20)	2 wks after SRS (n = 20)	3 mo after SRS (n = 5)
37–20 Gy	31.6 ± 16.2	33.6 ± 15.9 (6)	31.4 ± 17.2 (–1)
20–5 Gy	35.0 ± 11.2	35.8 ± 14.6 (2)	34.5 ± 17.5 (–1)
5–2 Gy	38.2 ± 10.6	36.5 ± 11.3* (–4)	35.4 ± 15.1* (–7)

Data are presented as mean ± SD
ROI, region of interest, CBF, cerebral blood flow; SRS, stereotactic radiosurgery
Numbers in parentheses are mean percent changes to prior to SRS
n = number of lesions
*statistically significant decrease to prior to SRS, $p < 0.05$

Data Analysis

The CT scans with superimposed isodose distribution obtained at radiation planning and the quantitative SPECT images were transferred to a SGI workstation (Indy R5000, Silicon Graphics, Mountain View, CA). Co-registration was then performed with a software package (Dr. View; Asahi Kasei Joho System, Tokyo, Japan). Regional CBF was evaluated according to four irradiated dose levels. Referring to the isodose distribution on CT images, regions of interests (ROIs) were manually placed over the 37–20 Gy dose area, 20–5 Gy dose area, 5–2 Gy dose area and less than 2 Gy dose area on the quantitative SPECT image. Circumscribed ROIs were set in 37–20 Gy, 20–5 Gy and 5–2 Gy dose areas on the slice including the center of radiation (Fig. 1). In the less than 2 Gy dose area, a total of 14–16 arbitrarily shaped ROIs were set in the bilateral upper and lower frontal cortices, parietal cortex, temporal cortex, occipital cortex, basal ganglion, thalamus, and cerebellum (Fig. 2). For each region, mean values of the ROIs were assessed. Statistical analysis was performed by the paired t-test. $p < 0.05$ was considered significant.

RESULTS

No patient developed recognizable clinical complications during the SRS and follow up period. The data from the mean and regional CBF measurements are shown in Tables 3–5. The mean CBF values before, 2 weeks after, and 3 months after SRS were 46.0 ± 6.2 m*l*/100 g/min, 42.7 ± 5.0 m*l*/100 g/min and 43.0 ± 5.6 m*l*/100 g/min, respectively. There was a significant reduction both at 2 weeks and at 3 months after treatment, of 7% compared to

Table 5 Changes of regional CBF in less-than-2 Gy dose level

ROI	Regional CBF (m*l*/100 g/min)		
	Prior to SRS (n = 13)	2 wks after SRS (n = 13)	3 mo after SRS (n = 5)
Upper frontal cortex	54.2 ± 11.5	50.4 ± 11.4 * (–7)	50.5 ± 8.1* (–7)
Lower frontal cortex	54.0 ± 10.5	49.5 ± 9.5* (–8)	48.4 ± 9.5* (–10)
Temporal cortex	52.9 ± 9.7	48.5 ± 9.8* (–8)	45.2 ± 6.4* (–16)
Parietal cortex	55.8 ± 12.6	52.0 ± 10.2 (–6)	49.2 ± 9.8* (–12)
Occipital cortex	56.4 ± 10.2	49.8 ± 8.9* (–12)	45.0 ± 9.2* (–20)
Thalamus	49.0 ± 11.1	43.7 ± 11.5* (–11)	43.2 ± 9.4* (–12)
Basal ganglia	53.7 ± 7.2	47.6 ± 9.5* (–11)	49.3 ± 9.9* (–8)
Cerebellum	61.9 ± 12.4	53.1 ± 13.6* (–14)	48.6 ± 13.1* (–22)

Data are presented as mean ± SD
CBF, cerebral blood flow; SRS, stereotactic radiosurgery
Numbers in parentheses are mean percent changes to prior to SRS
n = number of patients
*statistically significant decrease to prior to SRS, $p < 0.05$

pretheraputic values (Table 3). There was no significant regional CBF change in the areas receiving 37–20 Gy and 20–5 Gy after SRS. Significant regional CBF reduction was recognized in the areas that received 2–5 Gy and less than 2 Gy. In the areas which received 2–5 Gy, there were 5% and 7% reductions at 2 weeks and 3 months after the SRS, respectively (Table 4). In the areas that received less than 2 Gy, significant regional CBF reductions were recognized in almost all ROIs: 6–14% at 2 weeks after and 7–22% at 3 months after (Table 5).

DISCUSSION

SRS is being used as an alternative to, or in combination with, surgical excision of various intracranial lesions. Although the side effects are considered to be minimal, little is known about the subclinical toxic effect on the normal brain. The primary effect of radiation on the central nervous system is caused by vascular damage.[5–7] The effects of SRS on lesions are supposed to be similar to those described in normal vessels after high-dose irradiation, which have been well documented in humans and in laboratory animals.[9,10] The earliest lesion appears to be endothelial damage, which is evident within days after treatment. Then relative reduction in microvessel flow occurs almost at the same time, with a further decrease weeks after radiation.[11] Months or years later, vessels develop concentric or eccentric narrowing of their lumina, with intimal fibrous proliferation, foam cell accumulation, and hyalinization of vessel walls. These changes represent nonspecific responses to vascular injury and resemble certain aspects of atherosclerotic and traumatic lesions.

In this study, we assessed regional CBF change in the target area and out-of-field of radiation by means of ^{99m}Tc-HMPAO scintigraphy and the Patlak plot method. According to Matsuda,[12] intra-subject change from the first to second examination (within 3 months) of hemispheric CBF obtained by the Patlak plot method was –0.05 m*l*/100 g/min (–0.02%). For the reproducibility of regional CBF obtained from ^{99m}Tc-HMPAO SPECT, it has been reported that the differences between the first and second session (at an average interval of 3 months) of each region in the brain ranged from –1.3 to 4.2%.[13] These data indicate that the CBF measurement with ^{99m}Tc-HMPAO and the Patlak plot method has satisfactory reproducibility.

In our study, no significant regional CBF change was noted in the areas which received 37–20 Gy and 20–5 Gy. The former areas were corresponded to the targeted lesions themselves, such as tumors or AVMs. And the latter areas mostly contained perilesional edema. The pre-SRS regional CBF values were 31.6 ± 16.1 m*l*/100 g/min in the areas which received 37–20 Gy and 35.0 ± 11.7 m*l*/100 g/min in the areas which received 20–5 Gy. These low CBF values imply that little normal brain tissue was contained in these areas. Although ^{99m}Tc-HMPAO cannot evaluate the blood flow of irradiated tumors or AVMs, our data simply suggest that there was no significant change in perfusion of normal brain tissue in these areas.

There was significant regional CBF reduction in the areas with 5–2 Gy and less than 2 Gy of exposure. This unexpected result of CBF reduction after such low doses of irradiation could be explained from the report of an animal experiment[14] in which loss of small capillaries occurred after irradiation doses as low as 2 Gy. Moreover, reduction of regional cerebral blood volume (CBV) by about 23% was documented on a human MRI study[15] in the extra-target brain areas after fractionated stereotactic radiotherapy. Regional CBV reduction in this case indicates that loss of capillaries and subsequent reduction of regional CBF may occur in brain even at low dose exposure. On performing SRS for multiple lesions in the same patient, the received dose in out-of-field of radiation becomes higher than in the case of the treatment of a single lesion. Much care should be taken with such patient.

In our series, among the areas which received less than 2 Gy, more prominent regional CBF reduction was noted in the occipital cortex and cerebellum. There was no change in the size of targeted lesions or perilesional edema during the follow up period in the present study. The reason for the relatively high reduction rate in posterior circulation is difficult to give from previous literature. Further investigation will be needed if it is caused functionally, or by a difference in radiation sensitivity, or by other causes.

Comparison of measured data with clinical and functional tests is required to evaluate the influence of regional CBF decline on quality of life and cognitive functioning after intracranial SRS. Neuropsychological testing may be able to assess this, if the onset of radiation-induced regional CBF change coincides with detection of impaired cognitive functioning. Our data indicate the need to monitor characteristic changes, or to quantify deficits in the intellectual capability of patients treated with SRS for intracranial lesions.

CONCLUSION

^{99m}Tc-HMPAO SPECT revealed subclinical CBF reduction after SRS in the normal brain in out-of-field of radiation. Mean CBF was significantly decreased by 7% at 2 weeks and 3 months after SRS. Significant reduction in regional CBF was observed in the areas receiving 0–2 Gy and 2–5 Gy at 2 weeks and 3 months after SRS, at most by 22%.

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