Combined Brachytherapy and External Beam Radiotherapy in Normal Monkey Brains

—Experimental Radiation Necrosis Evaluated by Sequential Magnetic Resonance Imaging—

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Abstract

Radiation-induced brain damage was evaluated using sequential magnetic resonance (MR) imaging in monkeys more than 1 year after either brachytherapy or combined brachytherapy and external beam radiotherapy (EBRT). MR images were obtained 1 week, 1 month, 3 months, and subsequently every 3 months after brachytherapy, and the volume of the lesions was measured. In all four monkeys receiving only brachytherapy and three of the four animals receiving combined brachytherapy and EBRT, MR imaging revealed only transient extensive edema 1 week after treatment and ring enhancement, which was maximal 3 months after treatment, surrounding the implantation site. In one of the four animals undergoing combined brachytherapy and EBRT, MR images obtained 9 months after treatment showed an irregularly extending enhanced lesion with edema. MR images obtained 15 months after brachytherapy in this monkey showed the lesion extended into the contralateral hemisphere through the corpus callosum. Necropsy revealed severe radiation necrosis. This animal developed a very similar MR imaging presentation to that often encountered in human brains after combined brachytherapy and EBRT.

Key words: iridium-192 brachytherapy, magnetic resonance imaging, monkey, radiation necrosis

Introduction

Stereotactic interstitial brachytherapy can selectively and effectively deliver high doses of irradiation to the tumor volume.^{3,8,11,12,21} In general, brachytherapy is combined with external beam radiotherapy (EBRT) to treat patients with malignant glioma.⁴ This combined therapy is effective and patients can achieve long-term survival, but focal radiation necrosis requiring resection of the lesion can seriously degrade the quality of life for up to one half of the patients.^{1,4,9,12,19,23,24} Understanding of the pathophysiology and/or prevention of focal radiation necrosis is important to improve both patient survival and quality of life. However, the association of brain damage with the combination of EBRT and

brachytherapy has not been investigated. Previously, we developed a monkey model for brain damage caused by interstitial irradiation using magnetic resonance (MR) imaging and histological analysis for evaluation up to 6 months after treatment.^{5,14} This model showed that tissues receiving more than 200 Gy were damaged, characterized by a peak of edema 1 week after irradiation and maximum radiation necrosis 3 months after irradiation. In particular, the edema observed during the acute stage after implantation was extensive relative to the size of the necrotic lesion. The correlation between the MR images and the results of histopathological analysis suggest that the high-intensity lesion seen on T₂-weighted MR images is related to edema and demyelination, and the ring enhancement seen on

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contrast-enhanced T_1 -weighted images is related to vascular changes and inflammatory responses. Furthermore, these results suggested that the central low intensity seen on contrast enhanced T_1 -weighted MR images is related to coagulation necrosis.

This study examined the normal brain response to combined EBRT and brachytherapy in the monkey model established in our institute.

Materials and Methods

I. Animals

Ten adult Japanese monkeys (*Macaca fuscata*) weighing 5 to 10 kg were housed individually under standard conditions at Okayama University Animal Care Facility, and received routine care by trained animal technicians. The experiment was carried out according to the Animal Experiment Guide of the Okayama University Medical School. The monkeys were divided into four groups at random: four animals received only brachytherapy, four received brachytherapy followed by EBRT, one received only EBRT, and one underwent a sham operation as the control.

Food but not water was withheld from the animals for at least 12 hours before the surgical procedures and radiological studies. The animals were anesthetized with ketamine hydrochloride (10 mg/kg) and atropine sulfate (0.06 mg/kg). An intravenous catheter was introduced into the saphenous vein, through which lactate Ringer's solution was infused throughout the procedure. The anesthesia was maintained with pentobarbital (15 mg/kg), administered

as an intravenous bolus, supplemented with 5 mg/kg as needed.

II. Brachytherapy

A longitudinal skin incision was made in the right frontal region. A burr hole (1 × 1 cm) was drilled 7 mm to the right of the midline and centered on a point 22 mm anterior to the interaural line. The dura mater was cut linearly. Under stereotactic guidance, a silicone catheter (Santo Medica, Tokyo), about 1 mm in diameter and 22 mm long and containing the iridium-192 source (Japan Radioisotope Association, Tokyo), was inserted through this burr hole into the brain. The catheter was then advanced 22 mm below the brain surface, perpendicular to the plane passing through the external auditory meatus and the inferior orbital ridge (the H-O plane) (Fig. 1).

The seed assembly was 21 mm long and 1 mm in diameter, and contained 13 or 14 seeds with an activity of 9.19 to 13.44 mCi (mean $\pm$ SD 11.82 ± 1.18). The total dose was calculated at a reference point with a computerized radiation treatment planner (Modulx; Computerized Medical Systems, St. Louis, Mo., U.S.A.). This reference point was 5 mm posterior to the midpoint of the iridium-192 source. Doses of 196.47 to 211.24 Gy (mean $\pm$ SD 202.32 ± 5.01) were delivered at the reference point at rates of 1.106 to 1.2658 Gy/hr (mean $\pm$ SD 1.1422 ± 0.0562) (Table 1). Only one of the four animals undergoing brachytherapy combined with EBRT received a smaller dose of 112.93 Gy (rate of 0.9108 Gy/hr). The iridium-192 source remained in the brains for 124–191 hours, depending on the activity.

Fig. 1 Diagrams showing the location of the stereotactically implanted iridium-192 source in the horizontal (left) and sagittal (right) planes. The right diagram also shows the relationship between the placement and the six axial magnetic resonance imaging slices. H-O plane: plane passing through both the external auditory meatus and the inferior orbital ridge.

Table 1 Radiation data for individual monkeys

Animal No.	Group	Brachytherapy*		EBRT**			TDF
		Dose (Gy)	Dose rate (Gy/hr)	Dose (Gy)	No. of fractions	Fraction size (Gy)	
1	brachytherapy	203.61	1.14	NA	NA	NA	NA
2	brachytherapy	211.24	1.11	NA	NA	NA	NA
3	brachytherapy	196.47	1.11	NA	NA	NA	NA
4	brachytherapy	197.58	1.11	NA	NA	NA	NA
5	sham operation	NA	NA	NA	NA	NA	NA
6	brachytherapy + EBRT	200.01	1.13	35	5	7	98
7 [#]	brachytherapy - EBRT	202.27	1.13	35	5	7	98
8	brachytherapy + EBRT	205.05	1.27	25	5	5	59
9	brachytherapy + EBRT	112.93	0.91	25	5	5	59
10	EBRT	NA	NA	35	7	5	82

*Dose and dose rate of brachytherapy are calculated at a reference point 5 mm away from the iridium-192 source.

**The external beam radiotherapy (EBRT) doses used in this study were calculated based on a time dose fractionation (TDF) biologically equivalent to conventional clinical doses, which range from 36 to 60 Gy when the irradiation schedule is five fractions a week and 2 Gy per fraction. [#]This animal had severe delayed radiation necrosis 12 months after brachytherapy. NA: not applicable.

III. EBRT

EBRT used an external beam cobalt-60 gamma ray apparatus (Toshiba Medical Inc., Tokyo). The animals were anesthetized with only ketamine hydrochloride and atropine sulfate. Four animals underwent EBRT 1 or 2 months after the brachytherapy procedure. Two of these four animals received a total dose of 35 Gy in five fractions twice a week (Table 1). The other two received a total dose of 25 Gy in five fractions twice a week. One other monkey underwent EBRT alone (35 Gy in seven fractions twice a week). The whole brain of each animal was irradiated with bilaterally-opposed fields, although the orbita was always shielded. The dose rate at the midplane was 0.526 Gy/min, and the source-axis distance was 75 cm.

IV. MR imaging

MR imaging used a 1.5 T Signa Advantage version 5.4 (GE Medical Systems, Milwaukee, Wis., U.S.A.). T₁-weighted images were taken using the spin echo method with repetition time 500 msec, echo delay time 13 msec, field of view 13 cm, 256 × 128 matrix, and 3 excitations, the T₂-weighted images used the fast spin echo method with repetition time 4000 msec, echo delay time 95 msec, field of view 13 cm, 256 × 128 matrix, and 2 excitations, and contrast enhancement used intravenous administration of 0.4 ml/kg of gadolinium-diethylenetriaminepenta-acetic acid. The extent of brain damage was measured on MR images acquired 1 week, 1 month, 3 months, and subsequently every 3 months after the interstitial irradiation. Six 3-mm thick axial images with inter-

slice gaps of 0.5 mm were taken parallel to the H-O plane (Fig. 1 right). The fourth scan from the bottom always included the reference point to show the depth of the source from the brain surface.

V. Volume analysis

Volume analysis was performed in the eight animals undergoing interstitial irradiation and in the control monkey. The lesions were divided into two distinct categories^{5,14)} according to the findings on MR imaging: Enhanced lesions equivalent to disruption of the blood-brain barrier or vascular change and containing a low-intensity lesion equivalent to necrosis on the T₁-weighted image, and high-intensity lesions equivalent to edema on the T₂-weighted image. Quantitative analysis of these lesions used an irregular region of interest outlined on each MR imaging slice with a trackball-guided cursor. The outlined area was then measured by the computer and multiplied by the slice thickness and interslice gap. The sum of the volumes obtained from all six slices provided the total volume of the lesion.

VI. Macroscopic and microscopic examination

Animals were sacrificed with an overdose of barbiturate and fixed by vascular perfusion with a mixture of 2% glutaraldehyde and 2% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4). The brain was then removed and observed macroscopically. Tissue samples were immersed and fixed for a week. The specimens were sectioned into slices 4.5 μm thick, placed on glass slide, and stained with HE.

Results

I. Brachytherapy

Beginning 5 to 8 days after implantation, two of the animals stopped eating and showed neurological deterioration, including motor weakness of the left foreleg and left hemianopsia. These symptoms were transient and improved within 1 month. One animal died suddenly 6 months after treatment but showed no abnormal neurological or gastrointestinal findings until the day before death. Macroscopic examination of the brain did not identify the cause of death. Early death of this animal could be attributed to his advanced age, because his body weight was much larger than other ones. The three remaining animals were observed for 13 to 17 months and survived without any deficit (Table 2).

T₂-weighted MR images obtained 1 week after treatment revealed extensive high-intensity lesions causing a mass effect surrounding the implantation site in the right frontal white matter. This edema had resolved by 1 month after brachytherapy in all animals, and did not increase during the 15 months after brachytherapy. T₁-weighted MR imaging with gadolinium showed ring enhancement with a central, low-intensity lesion. These vascular changes and necrosis reached a peak 1 to 3 months after brachytherapy. Thereafter, the ring-enhanced lesions remained stable and even shrank irregularly in some animals during the 15 months after brachytherapy (Fig. 2).

II. EBRT

The animal receiving EBRT of 35 Gy showed only mild symmetrical atrophy of both hemispheres on

the MR images obtained 9 months after irradiation. This animal died of anesthetic complications immediately after this MR imaging (Table 2).

III. Combined brachytherapy and EBRT

One animal, who had received brachytherapy of 200 Gy and EBRT of 35 Gy, died 7.5 months after brachytherapy and stopped eating during the 2 weeks before death (Table 2). Necropsy of the brain found no specific findings likely to have caused the deterioration. Histological analyses could not be performed due to tissue degeneration after death. In the second animal who had undergone the same treatment, T₁-weighted MR imaging with gadolinium obtained 9 months after brachytherapy revealed an irregularly enhanced lesion extending outside the ring enhancement. T₂-weighted imaging showed this lesion as an increased high-intensity area. This lesion progressively expanded into the surrounding brain tissue and involved the contralateral hemisphere through the corpus callosum. MR imaging performed 15 months after brachytherapy showed the development of a diffuse enhanced lesion, which was partially mass formation suggesting focal delayed radionecrosis and hemorrhage, and disappearance of the cerebral sulci indicating increased intracranial pressure (Fig. 3). This animal was sacrificed because of persistent blindness and loss of general activity after the final MR imaging and cerebral angiography 16 months after brachytherapy. Angiography of the right internal carotid artery showed segmental stenosis of the distal anterior cerebral artery. The MR imaging slice that correlated with the gross section was chosen for study (Fig. 4). The gross section revealed white coagulative

Table 2 Symptoms and survival in individual monkeys

Animal No.	Body weight* (kg)	Symptoms and signs	Time of onset	Survival time** (mos)	Final MR imaging study (mos)
1	5.1	transient appetite loss	5 days after implant	17 [#]	15 after brachytherapy
2	5	none	—	15 [#]	15 after brachytherapy
3	5.9	transient lt hemiparesis	8 days after implant	13 [#]	12 after brachytherapy
4	8	none	—	6	3 after brachytherapy
5	6.1	none	—	17	6 after explant
6	5.9	none	—	7.5	6 after brachytherapy
7 [#]	6.2	blindness	15 mos after brachytherapy	16	16 after brachytherapy
8	8	convulsion	21 mos after brachytherapy	21	18 after brachytherapy
9	6	none	—	24 [#]	21 after brachytherapy
10	10	none	—	9 after EBRT	9 after EBRT

*Body weights were measured on beginning experiments. **Survival time indicates the period from the completion of brachytherapy, except for animal No. 10. [#]This animal had severe delayed radiation necrosis. [#]These animals were alive at the time of this report. EBRT: external beam radiotherapy, MR: magnetic resonance.

Fig. 2 Serial magnetic resonance images in the animal receiving only brachytherapy (animal No. 1); at 1 week, 3 months, 9 months, and 15 months (left to right). T₁-weighted gadolinium-enhanced images (upper row) showing ring enhancement at 1 week and 3 months and irregular shrinkage of the enhancement on the images obtained 15 months after brachytherapy. T₂-weighted images (lower row) showing transient marked edema as a high intensity lesion on the image obtained 1 week after brachytherapy.

necrosis consistent with the implantation site and liquefaction necrosis with scattered hemorrhage near the implantation site and in the contralateral frontal lobe. Histological analysis showed marked coagulative necrosis and calcification surrounding the implantation site, correlated with central low intensity areas on T₁-weighted MR images with gadolinium, and diffuse astrocytosis with infiltration of macrophages and vascular proliferation with hyalinosis of vessel walls extending into adjacent brain tissue, correlated with contrast enhanced area on T₁-weighted MR images with gadolinium. Histological analysis also revealed various stages of hemorrhage in the specimens obtained from both frontal lobes (Fig. 5). High intensity areas on T₂-weighted MR images involved demyelination and gliosis, but the margin of this area seemed to be histologically obscure without any lesion-specific findings. One animal who had received brachytherapy of 200 Gy and EBRT of 25 Gy suffered continuous generalized convulsions 21 months after brachytherapy, and was sacrificed because it could no longer eat. Gross section revealed a small but fresh hemorrhage surrounding brachytherapy-induced coagulative necrosis. This relatively new hemorrhage might be responsible for status

epilepticus, but had not caused any mass effect on adjacent brain tissues. The remaining animal who had received brachytherapy of 113 Gy and EBRT of 25 Gy survived for 24 months without significant deficits. Sequential MR imaging of these animals found no findings of specific delayed changes within the irradiation fields.

IV. Volume analysis

The volume of edema on the T₂-weighted images and the enhanced lesions containing central necrosis on the T₁-weighted images with gadolinium were measured and assessed as a function of time after brachytherapy (Fig. 6). MR imaging showed that changes induced by brachytherapy were characterized as transient, marked, high-intensity lesions at the acute stage, and were self-limiting contrast-enhanced lesions. In the animal undergoing the sham operation, these volumes were much smaller, and were no longer measurable at 3 months.

Discussion

The present study, like our previous study of the adverse effects of brachytherapy on normal brain tis-

Fig. 3 Serial magnetic resonance images 6, 9, 12, and 15 months (left to right) after brachytherapy in an animal receiving combined brachytherapy and external beam radiotherapy (animal No. 7). T₁-weighted gadolinium-enhanced images (upper row) showing delayed radiation injury as an irregularly enhanced lesion extending outside the ring enhancement. T₂-weighted images (lower row) showing this lesion is accompanied by widespread high intensity areas.

Fig. 4 Correlation between an axial slice of the final magnetic resonance image (left) obtained just before sacrifice and the corresponding gross section (right) in animal No. 7. The magnetic resonance image shows the extent of brain damage to the contralateral hemisphere through the corpus callosum. The gross section shows the actual brain damage, including liquefaction necrosis and scattered hemorrhage surrounding the central necrosis.

sue up to 6 months after irradiation, found that necrotic lesions did not enlarge any later than 3 months after brachytherapy. The long-term study found that progressive radiation necrosis after brachytherapy, which is seen clinically in humans with malignant brain tumors, did not appear until 15 months after brachytherapy. The brachytherapy dose (200 Gy) and dose rate used in this study were calculated at a reference point 5 mm away from the source. The total dose at a point 10 mm away from the source was approximately 60 Gy. Therefore, the brachytherapy dose regimen was almost identical to that of the clinical brachytherapy protocol in our institute. Other studies have also reported that brachytherapy-induced lesions are characteristically well-demarcated and self-limiting more than 1 year after brachytherapy.^{2,7,17,18)}

This study also combined brachytherapy with EBRT in this monkey model of brachytherapy to simulate the clinical treatment of humans with malignant brain tumors. When translated into the conventional regimen on the basis of time-dose fractionation, the dose of fractionated EBRT used in this study was equivalent to a dose of less than 60 Gy.¹⁶⁾ Interestingly, one monkey who received brachytherapy followed by fractionated EBRT of 35 Gy had

Fig. 5 Photomicrographs showing coagulative necrosis, astrocytosis, and hyalinosis of vessel walls (animal No. 7). Upper figure also shows the brachytherapy-induced lesion showing diffuse astrocytosis with vascular proliferations (HE stain, $\times 200$). Lower figure also shows necrotic tissue in the contralateral hemisphere and hyalinosis of a vessel wall (HE stain, $\times 400$).

diffuse delayed radiation necrosis more than 9 months after the brachytherapy. Delayed radiation necrosis occurred in the adjacent tissue outside the ring enhancement, around the tissue that had higher accumulated doses, and then extended irregularly into the surrounding white matter similar to tumoral invasion. Furthermore, the marked edema seen on T_2 -weighted images recurred after the irregular ring enhancement. The MR imaging findings in this animal resembled those of patients with radiation necrosis after brachytherapy.^{13,19} Although these phenomena were seen in only one of four animals undergoing combined therapy, we suggest that they can be attributed to the synergistic effects of the combined radiotherapies. These phenomena did not occur in the animals receiving only brachytherapy, and the delayed changes were predominantly con-

fined to an area adjacent to the implantation site.²²⁾

The mechanism of tissue damage caused by combined treatment with brachytherapy and EBRT is complicated and unclear. Delayed cerebral radiation necrosis generally appears a year or more after irradiation with doses larger than 50 Gy. The rate of this event is directly proportional to the dose, and is inversely proportional to the number of fractions or time during which radiation is administered.^{15,20)} Furthermore, brachytherapy differs greatly from EBRT in its biological effects.¹⁰⁾ The interactions between these two modalities at the cellular level are poorly understood. Radiation necrosis is often seen within several centimeters of the intraparenchymal neoplasm treated by the irradiation. Therefore, peritumoral edema and previous damage induced by brachytherapy may increase the tissue susceptibility to EBRT.^{6,19)}

Increased awareness of delayed radiation necrosis in patients treated with combined radiotherapies is necessary. Surveillance MR imaging, although limited in differentiating radiation necrosis from tumor recurrence, is a sensitive tool for the early detection of brain damage from radiation. There are many unanswered questions concerning the precise mechanisms involved in the development of brain damage from radiation, but the present results suggest that this model is useful for investigating clinically relevant problems ranging from the long-term results after brachytherapy to the interactions of brachytherapy and EBRT.

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Fig. 6 Graphs showing the volume of contrast enhancement on T₁-weighted magnetic resonance images (upper row) and high intensity lesions on T₂-weighted images (lower row) as a function of time after brachytherapy in animals undergoing only brachytherapy (left column) and combined brachytherapy and external beam radiotherapy (EBRT) (right column). The volume of enhancement did not enlarge after 3 months in animals receiving only brachytherapy, and the volume of edema peaked 1 week after treatment. One animal undergoing brachytherapy of 200 Gy combined with EBRT had a higher volume of contrast enhancement and edema 12 and 15 months after treatment.

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Commentary

The authors report the response to brachytherapy and external beam radiotherapy (EBRT) in the monkey brain. Previously, they had reported that the tissues of monkey brain irradiated with more than 200 Gy were damaged, characterized by cerebral edema and radiation necrosis. Degree of edema peaked at 1 week, and radiation necrosis was most prominent at 3 months after the radiation therapy. In this study, they examined the response to combined brachytherapy and EBRT in the monkey brain. In one of four monkeys, MR images showed diffuse radiation necrosis 9 months after the treatment, similar to that often encountered in human brain after combined brachytherapy and EBRT. There remains a question why radiation necrosis was not observed in the other three monkeys. Recently, their colleagues have reported the effect of combined brachytherapy and EBRT on patients with malignant gliomas.¹⁾ The mean dose of brachytherapy in their clinical practice was almost the same as that in the monkey models. Incidence of the late onset symptomatic radiation necrosis was similar with that obtained in the monkey model. I agree that this monkey model is useful for investigating radiation-induced brain damage after brachytherapy.

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The authors have performed a careful analysis of the effects of brachytherapy on the monkey brain when used alone or in conjunction with external beam radiotherapy. They found that transient cerebral edema developed in monkeys undergoing brachytherapy. However, one monkey who received both brachytherapy and external beam radiotherapy developed profound edema, and radiation necrosis as confirmed by necropsy. The authors should be commended for their documentation of the MR imaging changes that occur in the brains of monkeys following radiation in-

jury. The important message here is that combined radiation therapies have the potential of inducing severe radiation necrosis more so than brachytherapy alone. Their model will be very useful in continuing to increase our understanding of the time sequence of radiation injury to the brain post-treatment.

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This article evaluates the radiation-induced brain damage after brachytherapy or combined external beam radiotherapy in the monkey brain using sequential magnetic resonance imaging for more than one year. Acute change was already recognized one week after treatment and prolonged for 3 months as the

ring enhancement effect. As a late phase effect, irregularly extending enhanced lesion with edema was observed around 9 to 15 months after irradiation. Such necrosis was confirmed by histological findings from the specimens. As we often face difficulties in distinguishing between radiation necrosis after irradiation and tumor recurrence, this study will help us to get further information to evaluate it. Though the authors used high irradiation dose to the brain, we cannot discuss the very late effect of irradiation for the brain. Nowadays, in the clinical field we frequently discuss the quality of life for irradiated patients as long-term survivors, so we are hoping that the authors will perform a further experimental study of brain damage after low dose irradiation effects.

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