¹⁹²Ir Induced Radiation Damage in Monkey Brain Assessed with Magnetic Resonance Imaging and Histological Examination

Hisato HIGASHI, Kengo MATSUMOTO, Minoru NAKAGAWA,
Tomohisa FURUTA, and Takashi OHMOTO

Department of Neurological Surgery, Okayama University Medical School, Okayama

Abstract

The effects of irradiation on a large volume of normal brain tissue as occurs in interstitial brachytherapy were investigated. Double iridium-192 seed assemblies were stereotactically implanted into the right centrum semiovale of eight adult Japanese monkeys (*Macaca fuscata*). The morphological changes induced in the normal brain tissue were evaluated with magnetic resonance (MR) imaging with and without gadolinium-diethylenetriaminepenta-acetic acid (Gd) enhancement at 2 days and 1, 3, and 6 months after the brachytherapy. After each MR imaging examination, randomly selected experimental animals were sacrificed to analyze the histological changes. The low intensity area seen inside the ring of contrast enhancement on the T₁-weighted image with Gd enhancement was well correlated with histologically defined necrosis. The high intensity area seen outside the area showing contrast enhancement on the T₂-weighted image was well correlated with an area of histological edema and demyelination. The sizes of the lesion and the high intensity area were maximum during the acute stage (2 days) following interstitial irradiation. This monkey model with MR imaging can be used to investigate the development of brain damage induced by interstitial irradiation. We further recommend careful monitoring to detect the development of brain edema during the acute stage after interstitial brachytherapy, especially when large tumors are treated.

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

Introduction

Interstitial brachytherapy has been used recently in the treatment of malignant brain tumors, and has unequivocal value in patients with malignant glioma.^{10,12,13,21,25,28)} However, only 30–40% of patients with malignant gliomas qualify for brachytherapy because the tumor location, volume, configuration, extent, or patient performance status might contraindicate this therapy.^{2,10,17)} Tumor volume is one of the most important limiting factors. A larger tumor will expand and thereby extend the irradiated field into surrounding normal brain tissue. Additionally, a large irradiated volume may exacerbate the problem of radiation damage with delayed deterioration

in 22% of treated patients with low and high grade gliomas.^{15,31,32)} The incidence and severity of these changes were related to the volume of irradiated tissue.

Previous experimental studies used small, single radioactive isotopes in the non-primate brain and irradiated small volumes of tissue.^{1,3,9,11,26,33)} There is little quantitative data on the effects of interstitial irradiation of large volumes of normal brain. In this study, the right hemisphere of adult monkey brain was exposed to interstitial irradiation using double iridium-192 (¹⁹²Ir) seed assemblies. ¹⁹²Ir has a higher gamma energy and longer half-life than iodine-125, and the geometric attenuation is more constant,^{18,29)} allowing minimization of the dose rate factor during

Received September 9, 1994; Accepted February 7, 1995

Author's present address: H. Higashi, M.D., Department of Neurosurgery, Onomichi Municipal Hospital, Onomichi, Hiroshima, Japan.

the experiment. The principal advantages of this animal model are that large brain volumes can be irradiated, and that sequential observations of structural changes can be made noninvasively for later correlation with histological studies.¹⁹⁾ Additionally, extrapolation of the data to humans is more relevant because of the similarities between human and monkey brain.⁵⁾ We describe the quantitative determination of the effects of irradiation of a large volume of normal monkey brain using magnetic resonance (MR) imaging and histological examination to investigate the causes of radiation damage in patients with large tumors after brachytherapy.

Methods and Materials

I. Animals

Eight adult Japanese monkeys (*Macaca fuscata*) weighing 6.5–10 kg were housed individually under standard conditions at Okayama University Animal Care Facility and given routine care by trained animal technicians. The animals underwent a standardized neurological examination at various stages during the study. The animals were kept on a normal diet and housed in a radioprotective area during the irradiation period. This experiment was performed according to the Animal Experiment Guide,

Okayama University Medical School.

II. Interstitial irradiation

¹⁹²Ir seeds were supplied by the Japan Radioisotope Association (Tokyo). Each ¹⁹²Ir seed had a mean activity of 0.979 mCi (range 0.813–1.102 mCi). Each seed assembly measured 21 mm in length and 1 mm in diameter, contained between 11 to 14 seeds, and had a mean activity of 12.008 mCi (range 11.385–12.391 mCi). The planned dose of 225 Gy was calculated at the reference point using a computerized radiation treatment planner (Modulex; Computerized Medical Systems, St. Louis, Mo., U.S.A.). The reference point was 5 mm posterior to the mid-point of the posterior aspect of the seed assembly (Figs. 1 and 2). The mean dose rate delivered at the reference point was 133.719 cGy/hr (range 126.72–137.96 cGy/hr).

General anesthesia was required for the surgical implantation and removal of the ¹⁹²Ir assemblies. Preanesthesia included atropine sulfate (0.06 mg/kg) administered intramuscularly. Ketamine hydrochloride (10 mg/kg, i.m.) was used as the induction agent supplemented with diazepam and pentazocine. After anesthesia was established, the animal's head was fixed to a stereotactic frame. A right frontoparietal craniotomy (1 × 2 cm in size) was

Fig. 1 Projection of the stereotactic coordinates over the horizontal (left) and sagittal (right) views of the monkey brain showing the placement of the seed assemblies. The horizontal plane passes through both external auditory meati (interaural line) and through the inferior orbital ridge (H-O plane). Calculated doses of 225 Gy were delivered to the reference point (RP) 5 mm posterior to assembly (A) along the sagittal plane.

Fig. 2 Sagittal view of monkey brain superimposed on isodose curves for implanted seed assemblies. The reference point (RP) was 5 mm posterior to the posterior seed assembly along the sagittal plane. Bar = 10 mm.

performed and the dura mater was incised. Under stereotactic guidance,^{22,23} one seed assembly (A) was inserted into the brain 7 mm to the right of the midline, 22 mm deep to the brain surface, 22 mm anterior to the interaural line, and perpendicular to the plane passing through both external auditory meati and the inferior orbital ridge (H-O plane). Another seed assembly (B) was inserted parallel to the axis of assembly A, at the same distance from the midline, at the same depth, and 10 mm anterior to A (Figs. 1 and 2). The seed assemblies had approximately the same activity. The assemblies were removed approximately 7 days later (163–178 hrs), depending on the activity of the seed assemblies. During the irradiation period the animals were kept on a normal diet in a radioprotective area. Each animal received a prophylactic dose of carbenicillin sodium (20 mg/kg daily) administered intramuscularly from the start of the irradiation period and continuing for 7 days after removal of the seed assemblies.

III. MR imaging

MR imaging studies were performed with a MRT 200 (1.5 Tesla; Toshiba, Tokyo) under general anesthesia induced by ketamine hydrochloride (10 mg/kg, i.m.) and diazepam. T₁-weighted images (repetition time [TR] 600 msec, echo time [TE] 20 msec, field of view [FOV] 15 cm, 256 × 256 matrix, 2 excitations) with and without intravenous administration of 0.4 ml/kg of gadolinium-diethylenetriaminepenta-acetic acid (Gd), and T₂-weighted images (TR 2000 msec, TE 80 msec, FOV 15 cm, 224 × 256 matrix, 1 excitation) were used to

assess the extent and course of the tissue changes in normal brain. The images were acquired at 2 days (n = 8) and 1 (n = 6), 3 (n = 4), and 6 months (n = 2) following interstitial irradiation. Twelve contiguous 3 mm thick axial MR scans were taken parallel to the H-O plane, covering virtually the entire brain volume. One scan included the reference point²³; this was used to correlate morphological changes with radiation dose.

Lesions on the MR images were divided into three distinct areas: i) The contrast enhanced area (CEA) on the T₁-weighted image with Gd enhancement, ii) a low intensity area (LIA) inside this CEA on the T₁-weighted image, and iii) a high intensity area (HIA) on the T₂-weighted image outside the CEA. These areas were quantitatively analyzed by tracing the outline of the area on an acetate film placed over the image including the reference point. The outline of the brain, the sulcus, and the falx were traced. The CEA, LIA, and HIA were traced in different colors. The intensity gradient between the lesion (high signal) and normal brain (low signal) was very steep, so the boundaries were easily detectable. The tracings of the T₁-weighted image with Gd enhancement and the T₂-weighted image were superimposed so that the HIA outside the ring of enhanced tissue could be differentiated. The areas were measured using a PLANIX 5000 (TAMAYA Digitizing Area-Line Meter, Tokyo). All images were traced and measured by the same author.

IV. Histological examination

Immediately after each MR study two randomly selected animals were sacrificed with an overdose of barbiturate and perfused with a mixture of 1% glutaraldehyde and 1% paraformaldehyde in a 0.1 M phosphate buffer (pH 7.4). The brain was removed and grossly sectioned in the H-O plane, perpendicular to the axis of the seed assemblies, and parallel to the MR images. The sections were immersion fixed for at least 1 week. The specimens were sectioned into 8 μm slices. Slices were placed onto a glass slide and stained with HE. Selected sections at the level of the reference point were also stained with Klüver-Barrera's stain.

Some sections were chosen to include the reference point established under stereotactic guidance.^{22,23} These sections were used to calculate absolute doses at the edge of necrosis. Tissue shrinkage caused by fixation was assessed by comparing the size of the cerebral hemispheres measured along the long axis in the stained sections and in the corresponding MR images. The actual length of the necrotic area and the distance of the edge from the seed assemblies were

calculated. The absolute irradiation dose at the necrotic edge was then calculated for each animal.

Results

I. Neurological findings

Five days after seed implantation all animals showed some neurological dysfunction, including lethargy, loss of appetite, left hemianopsia, left hemiparesis, and ataxia. These signs worsened until 2–7 days after the seed assemblies were removed and then gradually improved. One month after seed

removal, no obvious neurological impairment could be seen.

II. MR imaging findings

The serial MR images are shown in Fig. 3. Two days after interstitial irradiation was completed, a CEA was observed around the placement tract of the seed assemblies. The T₂-weighted image showed a massive HIA in the white matter with midline shift. One month later, the LIA had increased in size and was surrounded by zones of contrast enhancement. The HIA and the mass effect were reduced. At 3

Fig. 3 Serial MR images of a monkey brain after interstitial irradiation. *Upper row*, T₁-weighted images with Gd enhancement; *middle row*, T₂-weighted images; *lower row*, T₁-weighted images. *Left column*, at 2 days; *left center column*, at 1 month; *right center column*, at 3 months; *right column*, at 6 months. Three and 6 months after treatment, a high intensity rim on T₁-weighted images, appearing as a low intensity rim on T₂-weighted images, was observed in all four animals. Histological examination revealed foci of acute and chronic hemorrhage.

months post-irradiation, the LIA had increased further in size and coalesced to form a single area completely surrounded by the CEA. A high intensity rim could now be seen on the T_1 -weighted image, which appeared as a low intensity rim on the T_2 -weighted image, and was observed in all four animals. Histological examination showed this rim to be foci of acute and chronic hemorrhage. Six months later the LIA had decreased in size, and the hemorrhagic lesion had become more apparent. The HIA had again enlarged in size.

Quantitatively, the total lesion size (HIA + LIA + CEA) was maximal 2 days after irradiation, rapidly decreased during the first 3 months, and

then tended to increase in the next 3 months (Fig. 4A). The HIA formed the largest part of the lesion at all times, constituting more than 50% of the total lesion, and its time course was the same as the total lesion (Fig. 4B). The LIA increased to the maximum during the 3 months after irradiation and then decreased (Fig. 4C). The CEA increased to the maximum during the first month (Fig. 4D).

The long axis of the CEA was maximum at 3 months, and therefore the absolute dose received at its inner and outer edges were calculated at this time. The minimum (outer edge) and the maximum (inner edge) doses of irradiation required to induce the CEA were 208.25 Gy (range 163–232 Gy) and 291.75

Fig. 4 Changes in the area of each part of the lesion over a 6 month period (2 days, $n = 8$; 1 mo, $n = 6$; 3 mos, $n = 4$; 6 mos, $n = 2$). The total lesion size (HIA + LIA + CEA) (A) and the HIA (B) were maximal 2 days after interstitial irradiation but rapidly decreased during the first 3 months. However, the area tended to re-expand over the last 3 months of the study period. The LIA (C) increased to a maximum during the 3 months after irradiation and tended to decrease thereafter. The CEA (D) increased to a maximum at 1 month after irradiation. Values are means $\pm$ SE.

Fig. 5 Photographs of gross Klüver-Barrera's stained sections showing the structural changes after irradiation. A, at 2 days; B, at 1 month; C, at 3 months; D, at 6 months.

Fig. 6 Photomicrographs of the CEA in cerebral white matter showing the microscopic changes after irradiation. Two days after interstitial irradiation, hemorrhage (*asterisk*), inflammatory cell infiltration, and fibrinoid necrosis (*arrows*) were present in the CEA (A). At 1 month, vascular proliferation (*arrows*) and fibrinoid necrosis (*arrowheads*) were seen (B). At 3 months, vascular proliferation, lipid-laden macrophages (*arrows*), and calcification (*asterisk*) were observed (C). After 6 months, hemorrhage (*asterisk*) and neovascularization (*arrows*) were observed (D). CN: coagulation necrosis. HE stain, A and D: $\times 100$; B and C: $\times 200$.

Gy (range 276–304 Gy), respectively (n = 4).

III. Histological findings

The LIA consistently had the histological characteristics of coagulation necrosis at all times (Figs. 5 and 6). The lesion was sharply demarcated from the surrounding brain tissue. The long axis of necrosis was maximum on the tissue section obtained 3 months after interstitial irradiation. The minimum dose of irradiation required to induce coagulation necrosis was calculated for this time. The mean dose at the necrotic edges was 235.5 Gy (range 228–248 Gy; n = 2). The HIA on T₂-weighted MR images correlated well with the pale-blue region on Klüver-Barerra's stained sections at all times (Fig. 5), and corresponded to histological areas of edema and demyelination. The CEA showed varied vascular damage, hemorrhage, and fibrinoid necrosis at 2 days (Fig. 6A), vascular proliferation and gliosis at 1 month (Fig. 6B), lipid-laden macrophages and calcification at 3 months (Fig. 6C), and neovascularization at 6 months (Fig. 6D).

Discussion

The response of normal tissue to irradiation at low dose rates is influenced by various physical and biological factors including the total dose, dose rate, irradiated volume, capacity to repair sublethal damage, and many cell cycle factors.¹⁴⁾ Most experimental studies^{1,2,9,11,26,33)} have used small irradiated volumes and therefore did not provide much quantitative data about the effects of a large irradiated volume on normal brain tolerance. In this study, large volumes of primate brains were irradiated using double ¹⁹²Ir seed assemblies, and serial MR imaging and histological data were obtained.

MR imaging can show brain damage not demonstrable by other neuroimaging methods and is particularly good at showing damage in the hemispheric white matter, which is the most frequent location for radiation-induced brain damage.^{16,27)} However, there is little data on serial MR imaging after interstitial brachytherapy.^{6,7,8,27,30,34)} Bernstein *et al.*^{1,3)} reported the breakdown of the blood-brain barrier (BBB) after iodine-125 interstitial irradiation in rat brain using serial MR imaging, a BBB tracer, and light and electron microscopy, but found the T₁- and T₂-weighted images showed little or no detectable lesion at any time. The white matter of non-primates is apparently too small to demonstrate changes induced by interstitial brachytherapy, but the monkey brain closely resembles the human brain and is large enough to be examined by MR imaging.

The radiation-induced lesions observed in this study were histologically similar to the changes recognized in human patients who developed late radiation damage.^{7,20)} The extent of the HIA and the LIA on the MR images correlated well with the lesions histologically identified as edema or demyelination and necrosis, respectively. The CEA was shown histologically to be an area of variable vascular damage, and this area seems to indicate the apparent BBB leakage. Oppenheimer *et al.*²⁴⁾ suggested that MR imaging has limited utility in assessing the impact of radiation on surrounding brain, but their study used postmortem fixed human brain, of which the water content may have been altered by formalin, thus decreasing the MR imaging sensitivity to the radiation changes.

Turowski *et al.*³³⁾ studied quantitative computed tomography (CT) and histological changes in the canine brain and found that the volume of the lesion rapidly increased for 1–4 weeks, followed by a generalized reduction. This time course differed from that seen in our study, where the total lesion size was maximal at 2 days. The lesion then rapidly decreased in size over the first 3 months, and then tended to re-expand until 6 months after irradiation. T₂-weighted MR imaging seemed to be more sensitive for demonstrating edema and demyelination than CT imaging.^{4,6,7)} Our results showed that edema was maximal in the very early stage following interstitial irradiation, and suggests that careful observation and appropriate therapy to control brain edema are required during the acute stage, especially when large tumors are treated.

Brain tissue necrosis was seen at each time point and expanded during the first 3 months after treatment. This time course is similar to that seen in patients with malignant glioma treated by interstitial brachytherapy.²¹⁾ Most of these patients had a central LIA on T₁-weighted images with Gd enhancement 1–3 months after therapy, which was histologically identified as coagulation necrosis occurring when the tumor was irradiated with more than 60 Gy.²¹⁾ In our study, the minimum dose required to induce necrosis was 235.5 Gy. This suggests that normal brain tissue is more tolerant to this type of irradiation than malignant glioma.

Several groups have observed the effects of interstitial irradiation on small irradiated volume model and found that the minimum radiation necrosis dose for normal brain is 180–270 Gy.^{1,9,11,26,33)} These results are quite similar to our large irradiated volume model and suggest that radiation dose is the primary factor influencing the irreversible damage to normal brain.

This monkey model is very useful for studying the effect of interstitial irradiation on normal brain tissue in combination with MR imaging to identify the histological changes induced. Future use of this model can investigate the dose volume effect, the dose rate effect, and the effects of radiosensitizers and tissue protective agents. Observation must be extended past 6 months to clarify the long-term effects of interstitial irradiation on normal brain.

Acknowledgments

We thank Dr. Katsumi Sakae (Department of Radiology, Okayama University Medical School, Okayama) for his help with the quantitative analysis, Dr. Tsuneharu Morito (Department of Radiology, Okayama University Medical School) for help with the dosimetry, Dr. Yasuhiro Harada (Department of Neurological Surgery, Okayama Citizen Hospital, Okayama), Mr. Iwao Takamoto and Mr. Souichirou Tadokoro for help with the MR imaging, and Dr. Yasuto Higashi (Department of Neurology and Neuropathology, Himeji Central Hospital, Himeji, Hyogo) for help with the histological analysis. We also gratefully acknowledge Dr. John R. Fike (Brain Tumor Research Center, University of California, San Francisco, Cal., U.S.A.) for his scientific suggestions.

References

- Bernstein M, Ginsberg H, Glen J: Protection of iodine-125 brachytherapy brain injury in the rat with the 21-Aminosteroid U-7489F. *Neurosurgery* 31: 923-928, 1992
- Bernstein M, Laperriere N, Leung P, MacKenzie S: Interstitial brachytherapy for malignant brain tumors: Preliminary results. *Neurosurgery* 26: 371-380, 1990
- Bernstein M, Marotta T, Stewart P, Glen J, Resch L, Henkelman M: Brain damage from ^{125}I brachytherapy evaluated by MR imaging, a blood-brain barrier tracer, and light and electron microscopy in a rat model. *J Neurosurg* 73: 585-593, 1990
- Brennan KM, Roos MS, Budinger TF, Higgins RJ, Wong STS, Bristol KS: A study of radiation necrosis and edema in the canine brain using positron emission tomography and magnetic resonance imaging. *Radiat Res* 134: 43-53, 1993
- Caveness FE: Experimental observations: Delayed necrosis in normal monkey brain, in Gilbert HA, Kagan AR (eds): *Radiation Damage in the Nervous System*. New York, Raven Press, 1980, pp 236-254
- Constine LS, Konski A, Ekholm S, McDonald S, Rubin P: Adverse effects of brain irradiation correlated with MR and CT imaging. *Int J Radiat Oncol Biol Phys* 15: 319-330, 1988
- Curnes JT, Laster DW, Ball MR, Moody DM, Witcofski RL: Magnetic resonance imaging of radiation injury to the brain. *AJNR* 7: 389-394, 1986
- Dooms GC, Hecht S, Brant-Zawadzki M, Berthiaume Y, Norman D, Newton TH: Brain radiation lesions: MR imaging. *Radiology* 158: 149-155, 1986
- Fike JR, Cann CE, Phillips TL, Bernstein M, Gutin PH, Turowski K, Weaver KA, Davis RL, Higgins RJ, DaSilva V: Radiation brain damage induced by interstitial ^{125}I sources: A canine model evaluated by quantitative computed tomography. *Neurosurgery* 16: 530-537, 1985
- Florell RC, MacDonald DR, Irish WD, Bernstein M, Leibel SA, Gutin PH, Cairncross JG: Selection bias, survival, and brachytherapy for glioma. *J Neurosurg* 76: 179-183, 1992
- Groothuis DR, Wright DC, Ostertag CB: The effect of ^{125}I interstitial radiotherapy on blood-brain barrier function in normal canine brain. *J Neurosurg* 67: 895-902, 1987
- Gutin PH, Leibel SA, Hosobuchi Y, Choucair A, Crumley RL, Edwards MSB, Wilson CB, Lamb S, Weaver KA: Brachytherapy of recurrent tumors of the skull base and spine with iodine-125 sources. *Neurosurgery* 20: 938-945, 1987
- Gutin PH, Leibel SA, Wara WM, Choucair A, Levin VA, Phillips TL, Silver P, Da Silva V, Edwards MSB, Davis RL, Weaver KA, Lamb S: Recurrent malignant gliomas: Survival following interstitial brachytherapy with high activity iodine-125 sources. *J Neurosurg* 67: 864-873, 1987
- Hall EJ: Radiation dose-rate: A factor of importance in radiobiology and radiotherapy. *Br J Radiol* 45: 81-97, 1975
- Leibel SA, Gutin PH, Wara WM, Silver PS, Larson DA, Edwards MSB, Lamb SA, Ham B, Keith AW, Barnett C, Phillips TL: Survival and quality of life after interstitial implantation of removable high-activity iodine-125 sources for the treatment of patients with recurrent malignant gliomas. *Int J Radiat Oncol Biol Phys* 17: 1129-1139, 1989
- Lo EH, Delapaz RL, Frankel KA, Poljak A, Phillips MH, Brennan KM, Woodruff KH, Valk PE, Steinberg GK, Fabrikant JI: MRI and PET of delayed heavy-ion radiation injury in the rabbit brain. *Int J Radiat Oncol Biol Phys* 20: 689-696, 1991
- Loeffler JS, Alexander E, Wen PY, Shea WM, Coleman CN, Kooy HM, Fine HA, Nedzi LA, Silver B, Riese NE: Results of stereotactic brachytherapy used in the initial management of patients with glioblastoma. *J Natl Cancer Inst* 82: 1918-1921, 1990
- Lucas GL, Luxton G, Cohen D, Petrovich Z, Langholz B, Apuzzo MLJ, Spozink MD: Treatment results of stereotactic interstitial brachytherapy for

- primary and metastatic brain tumors. *Int J Radiat Oncol Biol Phys* 21: 715–721, 1991
- 19) Lunsford LD, Altschuler EM, Flickinger JC, Wu A, Martinez J: In vivo biological effects of stereotactic radiosurgery: A primate model. *Neurosurgery* 27: 373–382, 1990
- 20) Martins AN, Johnson JS, Henry JM, Stoffel TJ, DiChiro G: Delayed radiation necrosis for the brain. *J Neurosurg* 47: 336–345, 1977
- 21) Matsumoto K, Nakagawa M, Higashi H, Maeshiro T, Tsuno K, Mishima N, Furuta T, Ohmoto T, Taguchi K, Nakagawa T, Hiraki Y: Preliminary results of interstitial ^{192}Ir brachytherapy for malignant gliomas. *Neurol Med Chir (Tokyo)* 32: 739–746, 1992
- 22) Mishima N, Tsuno K, Shigematsu H, Kunishio K, Matsuhisa T, Maeshiro T, Matsumoto K, Furuta T, Arimori M, Nishimoto A, Yoshioka J, Doi A: Radiation damage in normal monkey brain induced by brachytherapy with ^{192}Ir seeds (Part 2), in: *Abstracts of the 48th Annual Meeting of the Japan Neurosurgical Society*. 1989, p 40 (in Japanese)
- 23) Nakagawa M, Higashi H, Ono Y, Tsuno K, Shigematsu H, Maeshiro T, Matsumoto K, Furuta T, Ohmoto T: Effect of hyperthermia on the blood brain barrier of normal monkey brain, in: *Proceedings of the 6th International Congress on Hyperthermic Oncology*. 1992, p 176
- 24) Oppenheimer JH, Levy ML, Sinha U, El-Kadi H, Apuzzo ML, Luxton G, Petrovich Z, Zee C-S, Miller CA: Radionecrosis secondary to interstitial brachytherapy: Correlation of magnetic resonance imaging and histopathology. *Neurosurgery* 31: 336–343, 1992
- 25) Ostertag CB, Kreth FW: Iodine-125 interstitial irradiation for cerebral gliomas. *Acta Neurochir (Wien)* 119: 53–61, 1992
- 26) Ostertag CB, Weigel K, Warnke P, Lombeck G, Kleihues P: Sequential morphological changes in the dog brain after interstitial iodine-125 irradiation. *Neurosurgery* 13: 523–528, 1983
- 27) Packer RJ, Zimmerman RA, Bilaniuk LT: Magnetic resonance imaging in the evaluation of treatment related central nervous system damage. *Cancer* 58: 635–640, 1986
- 28) Scharfen CO, Sneed PK, Wara WM, Larson DA, Phillips TL, Prados MD, Weaver KA, Malec M, Acord P, Lamborn KR, Lamb SA, Ham B, Gutin PH: High activity iodine-125 interstitial implant for gliomas. *Int J Radiat Oncol Biol Phys* 24: 583–591, 1992
- 29) Sewchand W, Amin PP, Drzymala RE, Salazar OM, Salcman M, Samaras GM, Botero E: Removable high intensity iridium-192 brain implants: Technique and in vivo measurements in canine brain. *J Neurooncol* 2: 177–185, 1984
- 30) Spiegelmann R, Friedman WA, Bova FJ, Theele DP, Mickle JP: LINAC radiosurgery: An animal model. *J Neurosurg* 78: 638–644, 1993
- 31) Szikla G, Netti O, Blond S: Data on late reactions following stereotactic irradiation of gliomas, in Szikla G (ed): *Stereotactic Cerebral Irradiation*. Amsterdam, Elsevier/North-Holland, Biomedical Press, 1979, pp 167–174
- 32) Szikla G, Schlienger M, Blond S, Daumas-Duport C, Missir O, Miyahara S, Musolino A, Schaub C: Interstitial and combined interstitial and external irradiation of supratentorial gliomas. Results in 61 cases treated 1973–1981. *Acta Neurochir [Suppl] (Wien)* 33: 355–362, 1984
- 33) Turowski K, Fike JR, Cann CE, Higgins RJ, Davis RL, Gutin PH, Phillips TL, Weaver KA: Normal brain iodine-125 radiation damage: Effect of dose and irradiated volume in a canine model. *Radiology* 158: 833–838, 1986
- 34) Valk PE, Dillon WP: Radiation injury of the brain. *AJNR* 12: 45–62, 1991

Address reprint requests to: H. Higashi, M.D., Department of Neurosurgery, Onomichi Municipal Hospital, 3–1170–177 Shintakayama, Onomichi, Hiroshima 722, Japan.