Preliminary Results of Interstitial ^{192}Ir Brachytherapy for Malignant Gliomas

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Abstract

Twenty-six patients with recurrent or unremovable malignant gliomas were treated by interstitial brachytherapy with iridium-192 seeds. Stereotactic implantation of the afterloading catheters using the Brown-Roberts-Wells computed tomography (CT)-guided stereotactic system was performed in 24 patients and surgical implantation in two patients with pontine glioma. The response to therapy was measured by serial CT, magnetic resonance imaging, and clinical examination. Tumor regression was seen in 17 patients 1-3 months after implantation. Tumor progression was seen in only three patients. After interstitial brachytherapy, the most commonly observed CT finding was central low density. Median survival time was 18 months after implantation. Autopsies in five patients revealed the delayed effects of radiation injury such as typical vascular changes, microcalcification, and coagulative necrosis in the implant area and tumor recurrence at the periphery. The results suggest that brachytherapy is not curative but prolonged the median survival time by 6 months.

Key words: interstitial brachytherapy, iridium-192, malignant glioma

Introduction

Malignant gliomas are refractory to surgery, radiation therapy, chemotherapy, or combined therapy. Any recurrence is extremely difficult to cure. Initial control of the disease is much better as almost all these tumors recur locally.^{15,27,30)}

Interstitial brachytherapy is a method that maximizes irradiation to the tumor and minimizes irradiation to the surrounding normal tissue by placing the radiation source directly into the tumor. Interstitial low-dose irradiation (brachytherapy), either alone or combined with external beam irradiation, is the treatment of choice for many human cancers, including head and neck, gynecologic, and genitourinary tract carcinoma.³⁾ The interstitial brachytherapy has also recently been applied to malignant gliomas,^{4,5,7,9,10,13,26,31)} but the efficacy is not yet established.^{4,12,21)} The computed tomographic (CT)

findings after interstitial brachytherapy for brain tumors have not been extensively described.^{22,32,33)} Thus, it is important to investigate sequential CT changes after brachytherapy to evaluate the tumor response.

We report the evaluation of 26 patients with malignant gliomas treated with iridium-192 (^{192}Ir) interstitial brachytherapy and followed by serial CT and magnetic resonance (MR) imaging. The pathological changes in both tumor and cerebral tissue after brachytherapy are also presented.

Clinical Materials and Methods

All patients in this study had either a recurrent or unremovable tumor with a histological diagnosis of malignant glioma and were treated with ^{192}Ir interstitial brachytherapy between June, 1987 and September, 1991. Recurrent tumors included residual tumors resistant to conventional external irradiation and chemotherapy. The treatment procedure was explained to and informed consent was obtained from

each patient.

The target volume was defined preoperatively as the enhanced lesion demonstrated by postcontrast CT and MR imaging. Stereotactic implantation of interstitial catheters was performed in 24 patients under local anesthesia using the Brown-Roberts-Wells stereotactic system. Two patients with pontine glioma underwent surgical implantation after biopsy. The number of catheters, the number of sources in each catheter, and the entry point of the catheter were designed to deliver 30–60 Gy to the periphery of the lesion.

After catheter implantation, a CT scan confirmed the catheter position. A postoperative CT scan and orthogonal skull radiographs assessed the position of the dummy seeds. The isodose distributions were scaled to allow for superimposition on the radiograph and post-implantation CT scan (Fig. 1). Radioactive ^{192}Ir seeds (0.7–1.0 mCi) were inserted into catheters, and the tube sealed. The dose rate ranged from 20–80 cGy/hr, depending on the implant geometry. The catheters containing seeds were removed within 10 days of implantation to decrease the possibility of infection. All patients received high-dose prednisolone (60 mg/day) and prophylactic antibiotics during interstitial irradiation.

The patients were evaluated by neurological examination, Karnofsky performance score, CT, and MR imaging at intervals of approximately 4 weeks. Disease progression was defined as an increase in lesion size on CT scans or MR images or a decrease in the Karnofsky performance score. The time to progression and survival time were measured from the first day of treatment. Survival curves were drawn using the Kaplan-Meier product limit method.¹⁷⁾

Fig. 1 Isodose distribution curves superimposed on an axial CT scan after a ^{192}Ir implant. Numerals 0, 1, 2, 3, and 4 indicate isodoses 40, 30, 20, 15, and 10 cGy/hr, respectively.

Table 1 Patient characteristics

Histology	No. of cases*	Age (yrs)		KPS		Median IFI (mos)
		Mean	Range	30–60%	70–100%	
Astrocytoma grade III	14 (10)	41.0	3–77	9	5	5.5
Glioblastoma multiforme	9 (8)	52.4	18–65	3	6	3.8
Anaplastic ependymoma	3 (1)	52.5	46–62	1	2	2

*Numerals in parentheses indicate recurrent cases. IFI: interval from initial therapy to brachytherapy, KPS: Karnofsky performance score.

Table 2 Site of implantation and tumor doses

Site	No. of cases	Maximal diameter of tumor (cm)	No. of catheters	No. of seeds	Radiation dose at periphery (Gy)
Frontal	10	3.0–5.0	2–6	6–36	12–50
Temporal	1	5.0	6	18	30
Parietal	5	4.0–6.5	4–10	15–94	30–55
Occipital	3	2.0–5.0	4–7	32–35	30–40
Deep	5	2.0–4.0	1–6	3–24	30–50
Pons	2	3.0–4.0	1	12–15	11–30
Total	26	2.0–6.5	1–10	3–94	11–55

Results

A summary of the patients is shown in Table 1. There were 12 males and 14 females ranging in age from 3 to 77 years (mean, 47 yrs). Nine patients had glioblastoma multiforme, 14 had grade III astrocytomas, and three had anaplastic ependymomas. The Karnofsky performance score ranged from 30 to 100% (median, 80%). The interval between initial therapy to recurrence and subsequent brachytherapy ranged from 1 to 42 months (median, 5 mos).

The tumor location was the frontal lobe in 10 patients, the temporal lobe in one, the parietal lobe in five, the occipital lobe in three, the deep (basal ganglia, thalamus, pineal region) in five, and the pons in two. Seventeen patients had previously received surgery, total removal in six, subtotal removal in three, partial removal in five, and biopsy in three. Eighteen patients had previously received conventional radiation therapy (median dose, 50 Gy). Fourteen patients had received chemotherapy. Six patients had received interstitial brachytherapy during initial treatment.

The tumor size ranged from 2 to 6.5 cm in max-

Fig. 2 Serial postcontrast CT scans of patients with glioblastoma multiforme. *upper*: Before (*left*) and 2 months after (*right*) brachytherapy. Ring enhancement peripheral to the original lesion and a low-density area in the center are identified (*right*). The enhanced mass decreased in size compatible with original tumor. *lower*: Before (*left*) and 3 months after (*right*) brachytherapy in another patient with similar findings.

Fig. 3 Serial postcontrast T₁-weighted MR images of a patient with high-grade astrocytoma in the right parietal lobe before (*upper*) and 3 months after (*lower*) brachytherapy. Tumor regression can be seen.

imum diameter. The number of catheters for radioactive sources ranged from one to 10 and the number of seeds from three to 94. The radioactive sources were spaced at 1–2 mm, instead of the usual 1 cm spacing, which achieved a greater total activity and enhanced dose rate. The implant procedure was tolerated very well by all patients without any catheter-induced hemorrhages or seizures. The radiation dose ranged from 11 to 55 Gy at the tumor periphery and more than 100 Gy at the tumor center delivered over 10 days (Table 2).

Serial CT scans and MR images were obtained every month after implantation in most patients. CT scans 1–3 months after implantation demonstrated that the central enhanced region had been replaced by a low-density area in 18 patients (Fig. 2). In 17 patients, tumor regression was observed (Fig. 3), and the tumor had disappeared in three of the 17 patients (Fig. 4). In six patients, the tumor remained stable, but the lesion inevitably increased in size

causing increased mass effect and requiring increased steroid dosage or necrotomy. In three patients, clinical deterioration and an increased central low-density area with marked edema were observed 2 or 3 months after implantation. All three patients improved after craniotomy for debulking the mass. The mass histologically consisted of mixed necrosis and tumor. Outside the necrotic zone, tumor cells were observed, but the viability of the tumor could not be assessed. The occurrence of radiation necrosis correlated with total radiation dose and number of implanted radioactive seeds. The standard criteria for the evaluation of chemotherapy, such as complete remission, partial remission, *etc.*, cannot be applied to our series because of changes caused by radiation necrosis.

The median survival time was 18 months after implantation for both high-grade astrocytoma and glioblastoma multiforme (Fig. 5). Eleven patients have already died. In two patients, local control of the tumor was achieved. One died from subependymal spread and the other from pneumonia.

Autopsy was performed on five patients. Gross examination demonstrated central necrosis. Micro-

Fig. 4 Serial postcontrast T₁-weighted MR images of a patient with glioblastoma in the right basal ganglia before (*upper*) and 10 months after (*lower*) brachytherapy. The tumor disappeared 3 months after brachytherapy and no tumor recurrence was seen.

Fig. 5 Kaplan-Meier plot of the probability of survival from date of implantation for 14 patients with high-grade astrocytoma (*solid line*) and nine glioblastoma multiforme (*dotted line*). The numerator represents the number of patients who were still alive at the time of analysis.

scopic study revealed a well-demarcated transitional zone between the necrosis and surrounding viable tissue. The enhanced regions on CT scans showed pronounced vascular changes associated with coagulative necrosis (Fig. 6). Fibrinoid necrosis of the vessel walls and endothelial proliferation were observed. Microscopic edema was variably present in the infiltrated white matter. Calcification was observed in both necrotic and transitional zones in all cases. These changes were accompanied by macrophage reaction characterized by many foam cells containing sudanophilic lipid in the demyelinated tissue. Tumor cells, largely undifferentiated small cell types, were observed outside the completely necrotic zone, especially adjacent to blood vessels. In the necrotic zone, no tumor cells were observed. This histology was correlated with the available radiation dose data, showing that coagulative necrosis occurred in regions where the radiation dose exceeded 60 Gy.

Fig. 6 Section of the brain and photomicrographs of a tumor specimen from a patient with glioblastoma multiforme who died 3 months after brachytherapy due to pneumonia. A: Coronal section of the autopsy brain, showing well-demarcated coagulative necrosis. B: Transitional zone between the coagulative necrosis and viable tissue. HE stain, $\times 200$. C: Macrophage reaction characterized by the foam cells (arrows) and fibrinoid necrosis of the blood vessel wall. HE stain, $\times 400$. D: Microcalcification. HE stain, $\times 400$.

Discussion

Aggressive combined therapies excluding interstitial brachytherapy have not improved the prognosis for patients with malignant glioma. Still the median survival for patients with glioblastoma multiforme remains less than 1 year after diagnosis.^{27,31} Although over 90% of tumors are confined to a single area of the brain,¹⁵ surgery is not curative because the tumor usually infiltrates beyond the visible margins or into^{11,16,30} contiguous vital structures and cannot totally be removed. Chemotherapy is unsuccessful because of difficulties in achieving the tumoricidal concentration of the drugs within the tumor tissue and tumor resistance to specific drugs.²⁰ Radiation therapy is limited by both tumor insensitivity and radiation toxicity to normal brain tissue.^{3,19} Necrosis of normal brain prevents the delivery of more than 60–70 Gy by conventional teletherapy (external beam irradiation), doses too low to eradicate most tumors.^{3,19} Our experience shows that implantation of iridium seeds allows a high-radiation dose to be given while preserving the

surrounding normal brain. No incidents of infection, cerebrospinal fluid fistula, or wound breakdown occurred.

The CT findings after interstitial brachytherapy for brain tumors have not been extensively described.³² Whether post-implantation CT scans can be used to identify tumor persistence, tumor recurrence, or radiation reaction has not been established.³⁴ This retrospective evaluation of serial CT scans and pathological changes demonstrated a consistent central low density resulting in ring enhancement. This finding agrees with previous reports.^{4,32,34} Within 2 months of therapy, a central necrotic zone with or without ring enhancement was identified in all patients.

The standard criteria for the evaluation of chemotherapy, such as complete remission, partial remission, *etc.*, cannot be applied to our series because of changes caused by radiation necrosis. However, the 65% response rate in our series seems comparable to response rates for the chemotherapy currently used to treat malignant gliomas, and the median survival of 18 months for our small group of

patients with glioblastoma multiforme, nearly half of whom are still alive, suggests that brachytherapy may be a promising modality of the treatment for malignant gliomas.

Two direct radiation-induced effects of interstitial brachytherapy should be anticipated. There is transient increase in edema around the irradiated site, which may produce a worsening focal neurological deficits or symptoms of elevated intracranial pressure. The second possible adverse effect of brachytherapy is the development of radiation necrosis around the implant site.^{11,34} In our series, localized tissue necrosis with marked mass effect occurred in three of 26 patients and these three patients underwent craniotomy for debulking mass 2–3 months after implantation. Combination with interstitial microwave hyperthermia is being used to try to lower the minimum tumor radiation dose required and increase the tumoricidal effects of radiation.^{23,25,28}

The few autopsies in this series showed demarcated coagulative necrosis and numerous vascular changes around the implant. There was no evidence of widespread radiation damage in the normal brain tissue. In all cases, calcification barely detectable by CT was observed at the radioactive implant site. Brain tissue calcification following external irradiation occurs rarely 21 months to 8 years after therapy.^{19,32} However, all autopsy cases in our series had developed focal calcification within 3–12 months. We previously reported focal calcification within 1 week after interstitial irradiation of monkey brains.²⁴ Tumor recurrence was observed in the periphery where the radiation dose was less than 60 Gy. The tumor cells were small, round, and had hyperchromatic nuclei. Tumors in the corpus callosum were particularly difficult to treat because of diffuse infiltration into the cerebral white matter bilaterally. The variability in tumor response was probably due to many factors: the variability of tumor types, the extent of brain involvement, differences in vascularity, amount of necrosis, surrounding edema, previous external irradiation, and chemotherapy.⁸ The ideal minimum tumor dose and the optimal implant volume relative to the tumor volume are yet to be determined. The mode of recurrence and autopsy studies after implantation show that the radiation dosage to the tumor periphery must be more than 60 Gy to eliminate the residual tumor.

The critical problem is accurate localization and dosimetry of the tumor. More accurate identification of the tumor borders is needed, possibly by CT and MR imaging and three-dimensional isodose distribution calculations. Recent autopsy reports¹⁵ of post-ir-

radiated glioblastoma patients indicate that the majority of tumor recurrences (or residual tumor) are within 2 cm of the original tumor mass. However, the potential extent of neoplastic cells far beyond the CT contrast enhanced mass may vary according to the site.⁶ Determination of the tumor border and therefore the volume for implantation is fundamentally dependent upon the CT enhanced outline. However, the accuracy of neuroimaging in delineating the margins of gliomas is conjectural.^{2,6,18} For surgical or local radiation therapy, each glioma must be uniquely modeled using three-dimensional geometry with special attention paid to the periphery. Recently, we found that MR imaging definition of tumor margins showed abnormal tissue extended into isodense areas on CT scans.

Experience with interstitial irradiation of brain tumors is currently limited to a few institutions,^{1,14,29} but additional clinical experience and basic research are necessary to address these fundamental questions. The small numbers and short follow-up presented here preclude any conclusions regarding efficacy. However, this study suggests that interstitial radiation therapy is not curative but is effective in prolonging the median survival time. Longer follow-up in a larger number of patients is necessary to determine the potential beneficial effect on overall patient survival. Experience with a large population of carefully monitored patients should be obtained to determine the value of interstitial brachytherapy in the treatment of malignant gliomas.

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