Brachytherapy of recurrent malignant brain tumors with removable high-activity iodine-125 sources

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Thirty-seven patients harboring recurrent malignant primary or metastatic brain tumors were treated by 40 implantations of high-activity iodine-125 (I125) sources. All patients had been treated with irradiation and most had been treated with chemotherapeutic agents, primarily nitrosoureas. Implantations were performed using computerized tomography (CT)-directed stereotaxy: I125 sources were held in one or more afterloaded catheters that were removed after the desired dose (minimum tumor dose of 3000 to 12,000 rads) had been delivered. Patients were followed with sequential neurological examinations and CT scans. Results of 34 implantation procedures were evaluable: 18 produced documented tumor regression (response) for 4 to 13+ months five, performed in deteriorating patients, resulted in disease stability for 4 to 12 months. The overall response rate was 68%. In 11 patients, implantation did not halt clinical deterioration.

At exploratory craniotomy 5 to 12 months after implantation, focal radiation necrosis was documented in two patients whose tumor had responded initially and then progressed, and in three patients whose disease had progressed initially (four glioblastomas, one anaplastic astrocytoma); histologically identifiable tumor was documented in two of these patients. All improved after resection of the focal necrotic mass and are still alive 10, 15, 19, 24, and 25 months after the initial implantation procedure; only one patient has evidence of tumor regrowth. The median follow-up period after implantation for the malignant glioma (anaplastic astrocytoma and glioblastoma multiforme) group is 9 months, with 48% of patients still surviving. While direct comparison with the results of chemotherapy is difficult, results obtained in this patient group with interstitial brachytherapy are probably superior to results obtained with chemotherapy.

KEY WORDS • interstitial brachytherapy • malignant brain tumor • astrocytoma • iodine-125 • stereotaxy • tumor therapy

Most malignant gliomas are localized to a single area of the brain: central nervous system (CNS) metastases from these tumors are uncommon and systemic metastases are rare. Many solid systemic tumors that are localized when they are detected can be cured by surgery and radiation therapy; however, even though this combination is the best known treatment for malignant gliomas, radiation toxicity to surrounding normal brain precludes delivery, by external beam irradiation, of doses that control (cure) localized disease.

The implantation of radioactive isotopes interstitially (brachytherapy) permits delivery of high total doses of radiation to localized tumor masses. Compared with conventional teletherapy, the higher therapeutic ratio of such radiation delivered interstitially might allow delivery of radiation "boosts" to brain tumors immediately after external teletherapy or might allow radical reirradiation when these tumors recur.

Even though it was not practiced extensively, interstitial brachytherapy has been used to treat brain tumors since the early 1900's. In the last several decades, particularly in Europe, several groups have gained extensive experience with the stereotaxic implantation of radioisotopes, primarily to treat low-grade gliomas. The integration of stereotaxic systems with computerized tomography (CT) scanners, with which tumor targets can be visualized and precisely implanted, the availability of possibly more effective radioisotopes, and the development of neuro-oncology into a clinical science with emphasis on long-term follow-up review and rigid criteria of response to
FIG. 1. Computerized tomography scan taken with the stereotaxic frame in position on a patient with a recurrent right frontal anaplastic astrocytoma. The four vertical posts on the plastic frame are visible (squares). The geometric center of the frame (small cross) is related to a target within the tumor (large cross) by the scanner’s computer. The coordinates of the frame’s center and the target are seen at the lower right.

therapy make the continued use and refinement of brachytherapy attractive for use against malignant brain tumors.

In this paper, we report the initial results of treating patients harboring recurrent malignant primary and metastatic brain tumors by the stereotaxic implantation of removable, high-activity iodine-125 (~125I) sources.

**Clinical Material and Methods**

*Patient Selection*

Solitary recurrent primary or metastatic tumors as large as 6 cm in the largest dimension were treated with brachytherapy if they were localized with distinct margins on CT scans. Diffusely infiltrative tumors, tumors with subependymal spread, or multifocal tumors were not treated with this technique. In general, because of the limited biological reserve of previously irradiated posterior fossa structures, only supratentorial tumors were implanted.

From December 3, 1979, to October 1, 1982, 37 patients who harbored recurrent malignant brain tumors were implanted 40 times with high-activity ~125I sources. The patients ranged in age from 3 to 68 years. All tumors had recurred after surgery and irradiation (3600 to 6700 rads). Twenty-six patients had been treated with chemotherapeutic agents at recurrence; some could not tolerate continued chemotherapy because of compromised bone-marrow reserves.

Eighteen patients harbored primary anaplastic astrocytomas, 13 had glioblastomas, three suffered solitary cerebral metastases from carcinoma of the breast or lung and one a metastasis from melanoma, a 3-year-old boy harbored a recurrent choroid plexus carcinoma, and one patient had a recurrent malignant meningioma. Except for a single anaplastic astrocytoma in the brain stem and cerebellum, all were supratentorial tumors.

**Implantation Technique**

A preimplantation CT scan was performed with contrast enhancement; measurements of tumor geometry were made with the software intrinsic to the CT scanner.* A target was chosen at the center of roughly spherical tumors. To deliver more uniform doses, sources were positioned along the axis of elongated (prolately ellipsoidal) tumors. The tumor periphery was assumed to extend 0.5 cm beyond the edge of the area of peripheral contrast enhancement. A sufficient number of ~125I sources to deliver approximately 1000 rads/day (30 to 50 rads/hr) to the tumor periphery were loaded into the catheter(s).

Implantation of sources in adults was performed under local anesthesia using the Leksell stereotaxic system† modified for use with the CT scanner (Fig. 1). This procedure has been reported previously. The ~125I sources were held in an afterloaded coaxial silicone catheter system that has been described elsewhere. The advantages of this system are that implanted high-activity sources can be removed after the desired dose has been delivered, and that the catheter holds sources at the correct target positions in the often necrotic tumor centers.

Patients were isolated in private rooms while the sources were implanted and were cared for by nurses

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* General Electric Model 8800 CT scanner manufactured by General Electric Co., Medical Systems Division, Milwaukee, Wisconsin.
† Leksell stereotaxic apparatus manufactured by Downs Surgical, Inc., 2500 Park Central Boulevard, Decatur, Georgia.
Brachytherapy of recurrent tumors

Sources and Dosimetry

The \(^{125}\)I sources (30 to 50 mCi) were supplied by special order from the manufacturer. A well ionization chamber with a sensitivity of \(2.3 \times 10^{-11} \text{ A/mg radon}^{-1}\) equivalent for the higher photon energies was used to calibrate sources. Because an absolute calibration factor is not yet available for \(^{125}\)I, the chamber reading was related to the activity stated by the manufacturer.

After sources were implanted, a CT scan was performed to confirm accurate placement of sources (Fig. 2), and orthogonal radiographs were taken to determine source relationships. A computer program converted position data and source strengths into dose rate contours in any plane. The implantation time for the desired dose was calculated, and sources were removed in a simple procedure under local anesthesia on the appropriate day. Dose rate contours were converted by the computer to total dose plots, which were scaled to match the magnification and to allow superimposition on radiographs (Fig. 3) and postimplantation CT scans.

Evaluation of Patients

Postoperatively, corticosteroid doses were adjusted as needed to improve neurological function and to reduce the symptoms of increased intracranial pressure. Because improvement caused by steroids can mimic response to interstitial irradiation, doses were increased only when required to treat clear clinical deterioration. In addition, attempts were made to reduce the steroid dose every 6 to 8 weeks if the patient was clinically stable or improving. Anticonvulsant agents were used when medically indicated.

Patients were evaluated by neurological examinations and CT scanning at intervals of 8 weeks, when possible, and graded on a scale of \(-2\) to \(+2\) (deterioration to improvement). Patients were considered evaluable if they were alive and available for their first evaluation 8 weeks after implantation. Response was defined as a definite improvement in at least one criterion in the same evaluation period if the corticosteroid dose was unchanged or decreased. Progression of disease was defined as definite deterioration in at least one criterion if the corticosteroid dose was unchanged or increased. Stable disease was defined as no change in either criterion if the corticosteroid dose was unchanged or decreased. Time to progression was measured from the day of implantation until progression was documented.

Results

Evaluable Patients

Six patients could not be evaluated. Four of these died of non-neurological causes such as pulmonary embolism and systemic metastases before the first evaluation period, one was operated on for a brain abscess that developed in the immediate postimplantation period, and one has not yet returned for the first evaluation at the time of this report. Thirty-four implantations in 31 patients were evaluable. Minimum (peripheral) tumor doses of 3000 to 12,000 rads were delivered to these patients from 44 to 282 mCi of \(^{125}\)I divided among one to three implanted sources; typically, dose rates were 20 to 100 rads/hr.

Response and Stabilization after Brachytherapy

Eighteen implantations produced responses for 4 to 13+ months, calculated as the time to tumor progression (Figs. 4 and 5); five implantations caused stabilization for 4 to 12 months. Among the group with clear positive responses to brachytherapy or whose disease...
stabilized were patients harboring anaplastic astrocytoma, glioblastoma multiforme, brain metastases from systemic cancer, and a choroid plexus carcinoma.

Two patients, one with a recurrent anaplastic astrocytoma and the other with a glioblastoma multiforme, responded initially for 5 and 10 months, respectively, then deteriorated and underwent exploratory craniotomy 11 and 10 months after implantation (Table 1). The preoperative CT scan of one patient, a 6-year-old boy harboring an anaplastic astrocytoma who had received 5400 rads interstitially, showed increased contrast enhancement and hemispheric edema; he was deteriorating clinically with hemiparesis and was steroid-dependent. At craniotomy, only focal radiation necrosis but no residual tumor was found at the implantation site. Four months after surgery he is doing well and is not being treated with steroids. The patient harboring a glioblastoma, a 20-year-old man who had received 10,000 rads interstitially, had a hard yellow mass indicative of radiation necrosis at the implantation site, but at the periphery there was clear, histologically verified, viable tumor. He is alive and being treated with steroids and chemotherapy 9 months after exploratory craniotomy.

**Tumor Progression**

Eleven implantations did not halt clinical deterioration as measured by our evaluation criteria. At the first evaluation period, patients who received three of these implantations (for recurrent anaplastic astrocytoma or glioblastoma) had radiographic evidence of the spread of tumor to distant sites in the brain; despite the fact that disease at the site of implantation was at least stable, they were rated as treatment failures. One patient was implanted twice, with delivery of 3000 rads and 7000 rads 2 months apart, for a recurrent cerebral metastasis from a malignant melanoma. Treatment did not halt the rapid growth of the tumor, and the patient died 3 months after the second implantation procedure.

Another patient is clinically stable and shows only mildly increased contrast enhancement on CT scanning 4 months after implantation. The disease progression in this patient and the five other patients in this group, all of whom received a high dose (minimum tumor dose, 9000 to 11,500 rads), is probably the result of the development of radiation necrosis and does not necessarily reflect tumor regrowth. Because of progressive deterioration and steroid dependence, three of these patients, all of whom harbored recurrent glioblastomas, underwent exploratory craniotomy 5, 12, and 12 months after the implantation procedure was performed (Fig. 6, Table 1). In two patients, hard yellow masses were resected from edematous white matter; in each instance, histopathological examination revealed radiation necrosis. The third patient had the same gross...
Brachytherapy of recurrent tumors

pathology, but residual glioblastoma multiforme tissue was found mixed with the necrotic tissue. After surgery, all three showed clinical improvement; postoperative CT scans showed much less contrast enhancement and no mass effect. Only the patient with the histological evidence of tumor tissue is being treated with steroids 5 months after surgery, and the dose is being tapered slowly. The other two patients, neither of whom is being treated with steroids, are doing well 11 and 12 months after surgery and 23 and 24 months after the initial implantation procedure, respectively. One of these patients has a moderately severe hemiparesis but is ambulatory.

Two other slowly deteriorating patients who probably developed radiation necrosis did not undergo exploratory craniotomy. Both had been irradiated externally and interstitially. Because of deterioration that was presumed to be the result of a recurrent anaplastic astrocytoma, a young woman was implanted with removable high-activity $^{125}$I sources 16 months after she had received a permanent implantation of a low-activity $^{125}$I source. Her progressive deterioration was partially controlled with steroids, but she died 9 months later of herniation following a seizure. At the time this patient was treated, we were inexperienced with this clinical picture and we did not perform an exploratory craniotomy for radiation necrosis. Autopsy was denied by the family. Because of the large doses of radiation to which her brain had been exposed, it is probable that she suffered from radiation necrosis. The second patient, who harbored an anaplastic astrocytoma and had responded to the initial implantation, began to deteriorate, and underwent reimplantation 6 months later but continued to deteriorate. He is alive but hemiplegic and vegetative 21 months after the second implantation. Further CT scans and surgery have been refused by his family. He, too, may have radiation necrosis.

**Summary of Results**

Eighteen of 34 evaluable implantations produced clear responses and five others caused disease stabilization, for an overall response rate of 68%. There were 11 patients in whom the disease continued to progress, but among this group were three patients who developed multifocal disease, three who had probable radiation necrosis, and three who were explored surgically and found to have radiation necrosis. The three patients with surgically confirmed radiation necrosis (all of whom had glioblastoma) and two others (of whom one had anaplastic astrocytoma, and the other glioblastoma) all responded initially and then had subsequent deterioration and eventual resection of focal necrotic tissue; these five patients are our longest survivors. All were improved by surgery and remain alive 10, 15, 19, 24, and 25 months after implantation (Table 1). Only one of these patients is deteriorating from the continued growth of recurrent tumor. Thus, initial progression measured by our criteria of response is by no means an indicator of lack of effective treatment because the criteria cannot be used to distinguish focal radiation necrosis from recurrent tumor. Based on our experience, it is probable that aggressive interstitial brachytherapy in previously irradiated patients with tumor recurrences will cause radiation necrosis, and that exploratory craniotomy for resection of a necrotic mass should be a planned sequel to implantation.

Because surviving patients are omitted from consideration, survival plots are meaningless in a patient group such as this in which 48% are still surviving. One measure of the success of $^{125}$I brachytherapy is the median follow-up time from implantation, which is 9 months for the glioblastoma group and 10 months for the anaplastic astrocytoma group. For the malignant glioma group as a whole, the median follow-up period is 9 months. These are not overall survival times, which

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Tumor Type* &amp; Location</th>
<th>External-Beam Dose (rads)</th>
<th>Minimum $^{125}$I Dose (rads)</th>
<th>Interval Implantation to Reoperation (mos)</th>
<th>Histo-pathology at Reoperation</th>
<th>Survival Since Implantation (mos)</th>
<th>Clinical Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>GM, rt parietal</td>
<td>6600</td>
<td>9500</td>
<td>12</td>
<td>necrosis</td>
<td>25+</td>
<td>hemiparesis; off steroids; incapable of self-care</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>GM, rt parietal</td>
<td>6000</td>
<td>10,000</td>
<td>12</td>
<td>necrosis</td>
<td>24+</td>
<td>no deficit; works as teacher/coach; off steroids</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>GM, rt parietal</td>
<td>5100</td>
<td>10,000</td>
<td>10</td>
<td>necrosis/tumor</td>
<td>19+</td>
<td>hemiparesis; receiving steroids &amp; chemotherapy; incapable of self-care</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>AA, lt thalamic</td>
<td>4600</td>
<td>5400</td>
<td>11</td>
<td>necrosis</td>
<td>15+</td>
<td>mild hemiparesis; in school, participates in sports; off steroids</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>GM, rt parietal</td>
<td>5900</td>
<td>11,000</td>
<td>5</td>
<td>necrosis/tumor</td>
<td>10+</td>
<td>hemiparesis; receiving steroids; incapable of self-care</td>
</tr>
</tbody>
</table>

*GM = glioblastoma multiforme; AA = anaplastic astrocytoma.
in all instances are much longer, but only the followup time after implantation for recurrence. Because 48% of these patients are still surviving at the time of this report, survival results will progressively improve. In addition, refinements in patient selection and in implantation techniques and our increasingly aggressive approach to treatment will improve survival times in new patients; only one of the 12 patients treated in the past 15 months has died.

Complications

Among the 40 implantation procedures, four patients experienced complications. One patient developed a brain abscess in the tumor bed that required craniotomy and long-term parenteral antibiotic therapy. One patient developed bacterial meningitis and was treated with antibiotic agents. One patient deteriorated abruptly within hours after implantation for her thalamic glioblastoma; mannitol and high doses of corticosteroids were needed to reduce severe operative edema. One patient had dehiscence of the surgical wound in her very atrophic scalp and required wound revision and skin grafting.

Discussion

Radiation from an interstitial source is delivered at dose rates (approximately 1 to 2 rads/min) that are low compared to the dose rates (approximately 200 rads/min) of radiation delivered by external beam from a linear accelerator or cobalt-60 source. Therapeutic low dose-rate radiation from an interstitial source, which spares normal tissue, can be delivered continuously over several days, whereas, to avoid necrosis of normal tissue, the same total dose administered at high dose rates from an external source must be divided into multiple fractions given over several weeks. The increased therapeutic ratio of interstitial radiation is a result of the superior capacity, compared to neoplastic cells, of normal cells to repair sublethal radiation damage, a process that is ongoing during low dose-rate exposures. The therapeutic ratio is improved also as a result of the rapid drop in radiation exposure at increasing distance from the implanted source (inverse square law) such that surrounding normal tissues are relatively protected.

Iodine-125 emits characteristic x-rays, the energies of which (27 to 35 keV) are far lower than the energies of radiation emitted by other isotopes, such as iridium-192 and gold-198, that are commonly used for brachytherapy of solid tumors. Therefore, radiation from implanted 125I sources is effectively attenuated by interposed tissues, which accentuates the sparing of normal tissues during brachytherapy. Moreover, less radiation penetrates through the skull during 125I interstitial irradiation of brain tumors, and radiation that does have sufficient energy to penetrate the thick bone of the skull can be effectively shielded. Therefore, surgeons, nurses, and other personnel can be protected with lead aprons, which are useless for protection against the enormously higher energies of radiation from other commonly used isotopes. Another advantage of 125I, possibly the result of the low energies, is its purported higher relative biological effectiveness compared with isotopes such as iridium-192. It has been shown that 125I is valuable for the brachytherapy of several types of systemic cancers, particularly carcinomas of the prostate and head and neck.

The dose rates of radiation from commercially available, low-activity (0.5 mCi) 125I sources used for brachytherapy of tumors at other sites are sufficiently low that, if they were implanted in reasonable numbers into fast-growing, malignant brain tumors, they would not slow tumor growth. Higher-activity 125I sources (approximately 40 mCi) that are useful for the brachytherapy of brain tumors are provided only by special order and at considerable expense. The low radiation energies from 125I, which make it a suitable isotope for brachytherapy, make calibration of sources difficult; the welded ends on the small tubular sources are sufficiently thick that they shield radiation along the source axis, which causes anisotropy in the radiation field and makes determination of precise dosimetry difficult.

Other difficulties inherent in determining precise dosimetry are independent of the isotope used; they are the result of our current inability to localize sources within the tumor on postimplantation CT scans and to use these data to determine dosimetry. If the technical means were available, isodose plots could be more accurately related to the tumor's geometry and position of the sources within the tumor than is possible at present. The system currently used to determine dosimetry is based on source positions that are read from orthogonal skull x-ray films, which of course do not provide an image of the tumor. We are developing computer programs that will allow the 125I isodose plots to be displayed on CT scans, which would give more accurate dosimetry and would greatly improve treatment planning because optimum position(s) of sources within the tumor could be predetermined.

The availability of integrated stereotaxic and CT scanner systems has made the implantation of isotopes into tumors at open craniotomy suboptimal for several reasons. Most importantly, it is frequently difficult to expose a glioma at craniotomy enough to be able to appreciate its geometry, and this inability makes the implantation of a suitable isotope array nearly impossible. However, CT-stereotaxy allows precise implantation of sources into targets selected from CT scans that show the exact shape and dimensions of a tumor. Because a craniotomy wound may take several hours to close, the radiation exposure of surgeons and nurses would be greater than necessary. Stereotaxic implantation of isotopes can be performed through small skin incisions and burr or twist drill holes in the skull, which can be closed with facility.

Serial CT scans and neurological examinations have been used extensively to evaluate the response of patients undergoing chemotherapy for brain tumors.
Brachytherapy of recurrent tumors

However, it is difficult to apply these end points to evaluate the response of patients treated by brachytherapy, mainly because the radiographic and the clinical picture of radiation necrosis or tumor regrowth cannot be differentiated.\(^3,8,17\) It has been shown that radioactive sources implanted into gliomas can cause the delayed onset of focally increased contrast enhancement and signs of cerebral edema on CT scans with concomitant neurological deterioration; in this setting, stereotaxic biopsies have been used to confirm the diagnosis of radiation necrosis.\(^28\)

The inability to use neuro-oncological end points makes it difficult to compare the effects of brachytherapy for brain tumors with the results of chemotherapy. Because of changes caused by radiation necrosis, standard criteria such as response rate and time from response to progression are not accurate measures of the efficacy of brain-tumor brachytherapy. Some of our patients, who had evidence of disease progression after brachytherapy and who were found to have radiation necrosis at exploratory craniotomy, have survived longer than patients who, based on our criteria, were judged initially to be responders. Certainly, if comparisons can be made, the 68% response rate in our series is comparable to response rates for the best chemotherapy regimens currently used to treat recurrent malignant gliomas,\(^10,20,21\) and the median follow-up period of 9 months for our small group of patients with recurrent glioblastomas, nearly half of whom still survive, suggests that brachytherapy is significantly better than chemotherapy for this disease.\(^10,20,21\) Furthermore, because of the large number of patients who continue to survive, the median follow-up period is constantly improving.

A direct comparison of brain-tumor brachytherapy with chemotherapy, however, is not of critical importance. This study was designed as a Phase II oncology trial to test the efficacy of removable \(^125\)I sources for the treatment of patients with recurrent malignant brain tumors, and the results stand well by themselves. Particularly intriguing are the several patients with localized recurrences treated with brachytherapy who, when they were operated on for resection of radiation necrosis, had no histologically detectable tumor. The two patients with recurrent glioblastomas who are still surviving without active disease 1 year after exploratory craniotomy and 2 years after implantation offer some hope that cure of localized recurrences of some glioblastomas might be possible. This is especially true if focal radiation necrosis is a surgically remediable problem. Some patients have excellent neurological improvement while their steroid therapy is being tapered completely off after resection of the focal necrotic mass; therefore, we are hopeful that this treatment will be efficacious. Our findings are in agreement with the limited literature on this subject.\(^4\) Patients treated by brachytherapy are at risk of developing focal radiation necrosis; the possibility that focal necrotic tissue will have to be resected should be anticipated in every patient.

The cure of any recurrent tumor is enormously difficult to accomplish. It is of course better to control the disease initially. For this reason we have begun a protocol through the Northern California Oncology Group; in an attempt to gain local control of what is predominantly a localized disease,\(^13\) patients are implanted with removable \(^125\)I "boosts" immediately after conventional external-beam irradiation. Walker, et al.,\(^36\) found step-wise increments in survival in patient groups receiving 5000, 5500, or 6000 rads of external-beam irradiation after surgery; however, all tumors recurred and all the patients died. Because it is known that higher doses of external-beam irradiation, which might theoretically lead to further increments of survival, put patients at an unacceptable risk of developing large-volume radiation necrosis,\(^36\) our implanted "boost" is designed to increase the radiation dose to the tumor while sparing surrounding normal brain tissue. "Boosts" may induce long-term remissions or even produce cures of localized malignant gliomas. The overall survival time and perhaps even the cure rate will be the important outcome for this study. The risk of focal radiation necrosis in the patients receiving "boosts" is unknown, but, based on our experience with patients in the series reported here, this complication should be surgically manageable. It is not possible to predict for the individual patient the extent of neurological deficit that might be caused by such aggressive therapy.

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