Recurrent malignant gliomas: survival following interstitial brachytherapy with high-activity iodine-125 sources

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The authors report survival data for the first 41 patients treated for recurrent malignant gliomas with interstitial brachytherapy at the University of California, San Francisco (1980–1984). Iodine-125 (~125I) sources were temporarily implanted using stereotaxic techniques. The median survival period for 18 patients with recurrent glioblastomas was 52 weeks after brachytherapy; two patients are alive more than 5 years after brachytherapy. The median survival period for 23 patients with recurrent anaplastic astrocytomas is 153 weeks after brachytherapy, with 10 patients alive more than 3 years and four patients alive more than 4 years after brachytherapy. Both groups did significantly better (p < 0.01) than groups of patients with the same diagnoses and similar general characteristics who were treated at recurrence with chemotherapy alone. Because of deterioration of their clinical condition and evidence of recurrence from computerized tomographic scans, 17 (41%) of 41 patients required reoperation 20 to 72 weeks after brachytherapy. Despite the invariable presence of apparently viable tumor cells mixed with necrotic tissue in the resected specimen, nine patients have survived more than 2 years after reoperation and two of the nine are still alive 4 years after reoperation. The authors conclude that brachytherapy with temporarily implanted ~125I sources for well-circumscribed, hemispheric, recurrent malignant gliomas is effective and offers a chance for long-term survival even though focal radiation necrosis can seriously degrade the quality of survival in a minority of patients.

KEY WORDS • astrocytoma • brain neoplasm • stereotaxis • brachytherapy • radiation therapy • glioblastoma multiforme

AFTER conventional treatment with surgery and external beam irradiation, malignant gliomas tend to recur at or within a few centimeters of their original site. Recurrent tumors tend to be locally invasive, metastases to other parts of the nervous system are uncommon and metastases outside the nervous system are rare. Despite the relatively localized nature of these lesions, the principal experimental treatment for recurrent malignant gliomas has been systemic chemotherapy, which is traditionally used for metastatic disease. Various chemotherapy regimens and reoperation have provided some palliation for patients with malignant glioma recurrences.

Interstitial brachytherapy has been effective for tumors of many types, including head and neck, breast, prostate, and gynecological tumors. Because many malignant gliomas recur locally and because radiation therapy is the most effective therapy for malignant gliomas, there has been considerable recent interest in interstitial brachytherapy for these tumors. The primary advantages of brachytherapy are the same for brachytherapy at any site (namely, the ability of an implanted radioactive source to deliver a high focal radiation dose that relatively spares normal tissues surrounding the lesion). The recent availability of computerized tomography (CT)-directed stereotaxic systems makes it possible to implant radioactive sources into brain-tumor targets with great precision. These techniques were used to implant high-
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activity iodine-125 ($^{125}\text{I}$) sources into locally recurrent, previously resected and irradiated anaplastic astrocytomas and glioblastomas in 41 patients. The long-term survival data for these patients are reported.

**Clinical Material and Methods**

**Patient Selection**

Solitary recurrent malignant gliomas were treated with brachytherapy if they were well circumscribed on CT scans. Tumor histology was determined by review of previously resected material and not by stereotaxic biopsy before implantation. Diffusely infiltrative tumors, tumors with subependymal spread, or multifocal tumors were not treated by this technique. Because of the limited biological reserve of previously irradiated posterior fossa structures, tumors in the brain stem and cerebellum were not implanted with a radiation source.

**Radiation Sources**

The $^{125}\text{I}$ sources (30 to 40 mCi) were calibrated in a well ionization chamber.* The calibration factor of the chamber was obtained by measuring sources that had strength calibrations based on measurements from the National Bureau of Standards. In general, the measured strength of a source was within the range of values given by the manufacturer for the batch of sources.

**Implantation Technique**

A preimplantation CT scan was obtained after administration of contrast medium and measurements of tumor geometry were made with software intrinsic to the CT scanner.$^t$ Targets within the tumor were selected, and the array of isotopes to be implanted was chosen to deliver 30 to 60 rads/hr to the periphery of the contrast-enhancing lesion or, in some instances, to an area 0.5 cm beyond the rim of contrast enhancement.

Sources were implanted in adults under local anesthesia and in children under general anesthesia. The high-activity $^{125}\text{I}$ sources were housed in afterloaded coaxial silicone catheters$^{24}$ that were implanted stereotaxically. In the initial phases of the study we used a Leksell stereotaxic system, modified for use with the CT scanner;$^5$ more recently, the Brown-Roberts-Wells CT stereotaxic system$^3$ has been used. With CT stereotaxic guidance, the catheters could be positioned accurately at the tumor targets through burr holes or twist-drill holes; the standard craniotomy exposure of the tumor was unnecessary. Catheters held $^{125}\text{I}$ sources at the targets in the often necrotic tumor centers (Fig. 1).

**Dosimetry**

After the implantation procedure, a CT scan was obtained to confirm that sources had been positioned accurately, and orthogonal radiographs were obtained to index the source relationships. A computer program converted the position data and the individual source strengths into dose rate contours that may be visualized in any plane taken through the tumor volume. The implantation time necessary to deliver the desired dose was calculated, and catheters were removed in a simple procedure under local anesthesia on the appropriate day.

**Patient Care and Evaluation**

At intervals of 8 weeks patients were evaluated with CT scans and neurological examinations. Corticosteroids, most commonly dexamethasone, were administered to improve neurological function and to relieve symptoms of increased intracranial pressure (ICP). Because improvement caused by steroids can mimic response to interstitial irradiation, doses were increased only when required to treat clear clinical deterioration, and attempts were made to reduce the steroid dose every 6 to 8 weeks if the patient was stable or improving.

Results of the tests were graded on a $-2$ to $+2$ (deterioration to improvement) scale.$^{42}$ Patients were included in the study if they were available for their first evaluation 8 weeks after implantation. Response was defined as a clear 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 a clear 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 meas-

* Model 6702 $^{125}\text{I}$ sources supplied by the Medical Products Division, 3M Co., St. Paul, Minnesota; isotope calibrator, Model 4050, manufactured by Radcal Corp., Monrovia, California.

† Computerized tomography scanner, Model 8800, manufactured by General Electric Co., Medical Systems Division, Milwaukee, Wisconsin.
TABLE 1
*Characteristics of 41 patients undergoing brachytherapy*

<table>
<thead>
<tr>
<th>Factor</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>histology</td>
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<tr>
<td>anaplastic astrocytoma</td>
<td>23</td>
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<td>glioblastoma multiforme</td>
<td>18</td>
</tr>
<tr>
<td>sites</td>
<td></td>
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<tr>
<td>frontal</td>
<td>13</td>
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<td>temporal</td>
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<tr>
<td>parietal</td>
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<tr>
<td>occipital</td>
<td>2</td>
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<td>deep</td>
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<td>age (yrs) for anaplastic astrocytoma</td>
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<td>range</td>
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<td>age (yrs) for glioblastoma multiforme</td>
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<td>90</td>
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<td>range</td>
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<td>irradiation</td>
<td>41</td>
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<tr>
<td>chemotherapy</td>
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<tr>
<td>minimum brachytherapy tumor dose (rads)</td>
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<tr>
<td>minimum brachytherapy dose rate (rads/hr)</td>
<td>25-100</td>
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</table>

Reoperation

A craniotomy and resection of a mass lesion at the implantation site was performed in some patients at various intervals after placement of the radiation source to relieve ICP and to reduce corticosteroid dependency. The decision to reoperate was made based only on what was considered to be good neurosurgical practice in the individual patient; no specific criteria such as the size of the mass lesion or the corticosteroid dose were applied. After the implications of focal radiation necrosis in these patients were recognized (see below), our posture with regard to reoperation became more aggressive.

Histopathological Study

The amount of tumor and necrotic tissue in the pathological material from reoperations was grossly estimated by quartiles; thus, 75% of the material may have been judged to be necrotic and 25% to be residual/recurrent tumor. Because these patients had histologically proven glial tumors, our estimation of the presence of recurrent or residual tumor was conservative. Radiation effects and florid gliosis can resemble tumor, so our criteria led to an estimate of the presence of residual or recurrent tumor in all patients. The viability of residual tumor could not be assessed by the means used.

Subclassification of residual/recurrent tumor was not attempted unless there was evidence of obvious anaplastic change toward a more malignant tumor. Because of sampling problems with treated tumors, we did not attempt to assess slight shifts in morphology. If a histopathological diagnosis of a moderately anaplastic astrocytoma had been established and glioblastoma multiforme was present in resected material, this change in morphology was noted.

Results

Patient Characteristics

Forty-four patients were treated for recurrent tumor between January, 1980, and April, 1984. Two patients underwent two implantation procedures. Three patients were not evaluable: two died of non-neurological causes before the first 2-month evaluation and the third developed a brain abscess in the immediate postimplantation period that required immediate reoperation. Of the 41 evaluable patients, 23 had anaplastic astrocytomas and 18 had glioblastoma multiforme; tumor histopathology was determined by review of previously resected material. The patients ranged in age from 5 to 65 years; the median age was 36 years for patients with anaplastic astrocytomas and 48 years for those with glioblastomas. All patients had a Karnofsky performance status of 70 or greater (range 70 to 100, median 90).

All patients had previously been irradiated by conventional means (range 4400 to 7050 rads, median 6000 rads), and 25 had received chemotherapy either in the adjuvant setting (immediately after external irradiation) or for a previous recurrence. The minimum tumor brachytherapy doses ranged between 5740 and 12,000 rads; dose rate varied between 25 and 100 rads/hr, with the most common dose rate at 40 to 50 rads/hr (Table 1).

Response to Therapy

Twelve of the 41 evaluable patients showed tumor regression and survived 23 to 281 weeks. Nineteen patients stabilized and survived 20 to 288 weeks, and 10 had initial disease progression, ultimately surviving 19 to 151 weeks (Table 2).

Survival after Brachytherapy for Recurrence

Evaluation of response to therapy is not a reliable indicator of the efficacy of brachytherapy because of the possibly misleading influence of focal radiation necrosis (see below). Survival period after treatment is a more direct index of the efficacy of treatment. By

TABLE 2
*Response to brachytherapy*

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of Cases</th>
<th>Range of Survival (wks)</th>
<th>Median Survival (wks)</th>
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<td>90</td>
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<tr>
<td>stable</td>
<td>19</td>
<td>20-288</td>
<td>80</td>
</tr>
<tr>
<td>progression</td>
<td>10</td>
<td>19-151</td>
<td>32</td>
</tr>
</tbody>
</table>
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limiting this series to the first 41 evaluable patients with malignant gliomas (treated as of April, 1984), sufficient time had elapsed after treatment of the last patient to make survival data meaningful. Survival was evaluated from the time of implantation for recurrent disease until death or the time of final analysis (March 1, 1986). Obviously, overall survival times were longer in all patients. For the two patients who underwent implantation twice, survival was measured from the first procedure.

The median survival period of patients with malignant glioma (anaplastic astrocytoma and glioblastoma multiforme) was 74 weeks after the initial implantation; survival data are shown as Kaplan-Meier plots in Fig. 2 left. Patients with glioblastomas had a median survival time of 35 weeks after brachytherapy, with two of 18 patients surviving for more than 5 years (Fig. 2 center). Median survival time for patients with recurrent anaplastic astrocytomas was 153 weeks (Fig. 2 right). Ten of 23 patients have remained alive at least 3 years, and four of the 10 were alive for more than 4 years. Kaplan-Meier survival curves for the 41 patients are plotted according to initial response in Fig. 3. There are no statistically significant differences between the survival times of patients who showed initial response, stabilization, or progression.

Survival after Chemotherapy in a Control Group

For purposes of comparison, we selected a group of patients with anaplastic astrocytomas or glioblastomas treated at our institution at first recurrence after surgery and radiation therapy (and sometimes adjuvant chemotherapy) with one of several chemotherapy regimens including PCV 3 (procarbazine, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), and vincristine), 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) and 5-fluorouracil (5-FU); 1-(2-chloroethyl)-3-(2,6-dioxo-3-piperidyl)-1 nitrosourea (PCNU); or BCNU, 5-FU, hydroxyurea, and 6-mercaptopurine. The period of survival of this group was plotted to serve as a comparison for the patients treated with brachytherapy in this series. Some patients in this comparison group received additional chemotherapy for subsequent recurrences after failing one of the regimens listed above.

There were 104 patients in the chemotherapy-treated group: 42 with glioblastomas and 62 with anaplastic astrocytomas. Ages ranged from 18 to 65 years with a median age of 35 years for patients with anaplastic astrocytomas and 46 years for those with glioblastomas.

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FIG. 4. Computerized tomography scans of a left parietal astrocytoma before (left) and 6 months after (center) brachytherapy, showing increased contrast enhancement around a low-attenuation center. The patient underwent reoperation and is stable on a low dose of corticosteroids 2 years after brachytherapy (right).

FIG. 5. Computerized tomography scans of a right parietal mixed malignant glioma before (left) and at 3 and 6 months after brachytherapy (left center and right center, respectively). The size of the radionecrotic zone and surrounding edema increased over this interval. The necrotic tissue was resected; the patient is stable and not receiving corticosteroids 3 years after brachytherapy (right).

TABLE 3

<table>
<thead>
<tr>
<th>Characteristics of chemotherapy comparison group</th>
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<tr>
<td>Factor</td>
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<td>histology</td>
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<td>median</td>
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<tr>
<td>range</td>
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All patients had a Karnofsky performance status of 70 or greater (range 70 to 100, median 80) (Table 3).

Median survival for the chemotherapy group was 36 weeks, which is significantly inferior to the survival for brachytherapy patients (Fig. 2 left). Chemotherapy patients with recurrent glioblastomas had a median survival period of 28 weeks, which is not strikingly different from that for brachytherapy patients, who did only slightly yet statistically significantly (p < 0.01) better (Fig. 2 center). In the group of patients treated with chemotherapy for recurrent anaplastic astrocytomas, the median survival time was 51 weeks. Brachytherapy in these patients produced significantly longer periods of survival (Fig. 2 right).

Quality of Survival after Brachytherapy

The median Karnofsky performance score was 90 (range 70 to 100) at the time of brachytherapy. At each
of the first three 8-week evaluation periods, the median Karnofsky score was 80 (range 40 to 100). Therefore, there was no severe deterioration in function for the group as a whole in the 6 months immediately following brachytherapy. A small minority of patients appeared to suffer the consequences of focal radiation necrosis related to brachytherapy or showed symptoms of early tumor regrowth. Of the 36 patients alive at 6 months after brachytherapy, two had Karnofsky performance scores of less than 70.

Reoperation

Six patients treated with brachytherapy for recurrent glioblastoma multiforme and 11 patients treated for recurrent anaplastic astrocytoma had reoperations 20 to 72 weeks (median 36 weeks) after implantation. All patients had deteriorating clinical conditions that required increasing corticosteroid doses. There was clear CT evidence of increasing mass effect and increased contrast enhancement around a region of low attenuation (Fig. 4) that roughly corresponded to the site of implantation, the region that received the highest radiation dose. The interval between radiation source implantation and CT evidence of deterioration was between 8 and 48 weeks (median 24 weeks). Clinical deterioration and increasing steroid dependency tended to occur concomitantly with CT changes, and radiographic and clinical deterioration tended to be progressive if reoperation was delayed (Fig. 5).

Eleven of the 17 reoperated patients showed clear improvement after reoperation, and their corticosteroid dosages could be reduced; six of these 11 could stop steroid treatment entirely. Corticosteroid doses could not be reduced in six of the 17 patients, however, and four of these patients died from recurrent tumor.

The tissue resected at reoperation included various amounts of apparent tumor and gross necrotic tissue (Fig. 6). There was no correlation between the amount of apparent tumor or necrotic tissue in the resected specimen and survival time, as determined by regression analysis (Fig. 7). All resected specimens had at least 25% apparent tumor, and some of these patients are long-term survivors. Two patients whose resected tissue contained 50% apparent tumor are alive more than 5 years after receiving brachytherapy for recurrence. These data suggest that tumor cells resected from the heavily irradiated volume near the implantation sites may maintain morphological integrity but have little or no proliferative capacity.

The survival times of patients who underwent reoperation after brachytherapy were far greater (median survival not yet reached) than the median survival period of patients not subjected to reoperation (35 weeks) (Fig. 8). This suggests that it is essential to address the problem of focal radiation necrosis after implantation. Obviously, it is difficult to draw firm conclusions from these data because the two groups are so diverse; in general, patients who did not undergo reoperation were treated early in this study before we would consider reoperation.
brachytherapy might be attempted in patients harboring recurrent glioblastomas that have the appropriate geometry because a better long-term survival rate may be achieved than is possible with chemotherapy.

It is obvious that a retrospective comparison of the brachytherapy and chemotherapy groups on which the above conclusions are drawn is complicated by several factors. Patients treated with brachytherapy, at least in the latter part of the series, were selected because their lesions had the appropriate geometry for interstitial irradiation. It is possible that chemotherapy patients had tumors that were larger or more diffuse, and the results would be biased in favor of brachytherapy; however, because the chemotherapy patients had a Karnofsky performance score of more than 70, this group is certainly not neurologically devastated. In fact, patients in the comparison group were treated with chemotherapy at their first recurrence, and brachytherapy patients included those treated for second and third recurrences. Therefore, the brachytherapy patients were a more “endstage” population, which is consistent with the experimental nature of the treatment, and this factor biases results against the brachytherapy group. Moreover, these were the earliest patients treated with brachytherapy before our techniques were completely refined, which would also bias survival results against brachytherapy patients.

If long-term control of previously irradiated recurrent malignant gliomas is to be achieved with brachytherapy, it seems clear that the major risk of treatment is focal peritumoral radiation damage to normal brain. Kiessling, et al.,38 and Ostertag, et al.34 reported clinical deterioration and changes in the CT scans of patients treated by permanent implantation of iridium-192 sources into previously untreated low-grade gliomas that are similar to changes seen in our patients. In those two series, however, deterioration tended to be temporary and self-limited. The apparently permanent, progressive, and more severe focal radiation necrosis seen in our patients is probably related to previous external irradiation given at maximum tolerated doses. Our patients were irradiated with temporary, high-activity sources at dose rates higher than those used by Kiessling and Ostertag and their coworkers.38,34 Therefore, a dose rate effect in normal brain might account for variations in normal tissue damage.5,16,17,20,30,34,53,55

The inability to differentiate focal radiation necrosis from regrowth of brain tumors on radiographic or clinical grounds in the months following interstitial brachytherapy makes it a difficult and perhaps pointless exercise to grade brachytherapy patients with the same criteria as are used for evaluation of chemotherapy regimens.11,23,28,39,34 This can be appreciated from the lack of a significant difference in length of survival seen in the various response groups (Fig. 3). It appears that early deterioration is sometimes related to focal radiation necrosis and not to tumor regrowth.

By performing a series of stereotaxic biopsies through lesions seen on CT scans, Daumas-Duport, et al.,11
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attempted to differentiate radiation necrosis from recurrent glioma in patients with clinical and CT evidence of deterioration after interstitial brachytherapy. They found that biopsy material obtained outside the “target volume” for the radioactive sources (that is, from outside the volume with a high dose) was reliably predictive of recurrence, while material from the “target volume” was not reliable for this purpose because heavily irradiated tumor may be difficult to differentiate from luxuriant reactive gliosis and because apparently viable tumor may degenerate into necrotic tissue.

Because surgical reduction of the cerebral mass lesion in combination with corticosteroid therapy appears to be the best available treatment for focal radiation necrosis, we do not rely on stereotaxic biopsy; rather we obtain a histopathological diagnosis from tissue removed during surgical resection for palliation of the mass effect. Tissue resected at reoperation was, for obvious reasons, always obtained from the central tumor region that received a high radiation dose, so histopathological examination invariably showed the presence of some necrotic tissue and apparent residual tumor (as found by Daumas-Duport, et al.11) that had no relation to subsequent outcome. Survival periods in many of our reoperated patients are long (Fig. 7), despite the fact that resected tissue from all patients contained apparently viable tumor in the central volume irradiated. Tumor cells in the central volume may not be clonogenic. This is analogous to the experience with biopsy of prostatic adenocarcinomas after interstitial brachytherapy. Apparently viable tumor in biopsy material is not a consistent predictor of outcome, particularly if the biopsy was performed within the first 2 years after brachytherapy. We are attempting to culture tumor cells from the resected tissue in vitro. There is some evidence that the ability of these cells to form colonies in vitro is related to their viability in vivo, which may be predictive for early tumor recurrence. We are also using positron emission tomography in attempts to correlate fluorine-18-fluorodeoxyglucose uptake with the histopathological findings at reoperation and with outcome.

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Resection of necrotic tissue effectively improves deterioration. The mass of tumor tissue and perhaps a rim of normal brain seems to provide a nidus that induces brain edema. Removal of dead cells from the brain is particularly slow compared with other sites. and reoperation after brachytherapy seems to have clear advantages. Reoperation improved the clinical status in some of our patients and allowed reductions in their corticosteroid dosages. Because of the improved survival times and few complications in patients undergoing reoperation for focal necrosis, the tendency is to reoperate earlier.

It is known that surgery alone for recurrent malignant glioma is palliative and may lead to longer survival times in some patients, particularly those with a Karnofsky performance score of at least 60 and an interval of 6 months between initial treatment and recurrence. Thus, reoperations may be responsible in part for the superior median survival time of the 17 patients who underwent repeat surgery compared to the control chemotherapy group.

Our results suggest that brachytherapy is promising for certain recurrent malignant gliomas. The experience gained in subsequently treated patients has allowed us to refine our criteria for patient selection. It appears that small (< 5 cm), well-circumscribed supratentorial lesions located away from the midline in patients with good neurological status are the most amenable to brachytherapy. With these refined selection criteria and with our newly implemented treatment-planning computer programs and our evolving implantation techniques, patients treated more recently should do even better than the patients reported here.

Major issues that must be addressed include the ability to define target volume accurately on CT scans or magnetic resonance images, the selection of the proper isotope for implantation, and the best array of implanted sources for the irradiation of these tumors. Moreover, the problem of focal radiation necrosis makes the selection of the proper brachytherapy dose of paramount importance. An attempt is being made to lower our current minimum tumor dose of 8000 rads by concurrent treatment with dose-modifying agents such as heath or platinum compounds. Both modalities have the potential to inhibit repair of sublethal radiation damage and therefore to increase dramatically the effect of radiation delivered at low dose rates. We are hopeful that combination protocols will lower the dose of radiation sufficiently to reduce or eliminate focal radiation necrosis.

Based on the results of this initial trial with recurrent gliomas, a controlled prospective trial under the auspices of the Northern California Oncology Group for brachytherapy of patients with newly diagnosed lesions has been initiated. These patients are treated with brachytherapy immediately after surgical resection and external irradiation of the tumor volume, a time when malignant gliomas are most localized and microscopic invasion of peritumoral brain is in the initial stage. This represents the optimum situation for interstitial irradiation of the lesion. The combination of localized external irradiation to kill neoplastic cells at the tumor margins along with additional radiation (boost) delivered to the central tumor volume by brachytherapy has proved successful in tumors of the head and neck, cervix, and breast with long-term local control the rule rather than the exception.

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References


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