Interstitial brachytherapy of primary brain tumors

Preliminary report

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Ten patients harboring inaccessible, slow-growing or recurrent malignant primary brain tumors were treated by the stereotaxic implantation of a radionuclide seed — iridium-192 ($^{192}$Ir) or gold-198 ($^{198}$Au) — either permanent or removable. The strength for $^{192}$Ir seeds was selected to deliver 10,000 to 12,000 rads to the periphery of the tumor, and that for $^{198}$Au seeds to deliver 4000 to 7500 rads. Three of the six patients treated with $^{192}$Ir showed objective responses lasting 8, 11, and 12 months, respectively; and one patient's disease stabilized for 18 months. Three of the four treated with $^{198}$Au showed responses lasting 5 months, 6 months, and 2 years, respectively. Because of the higher dose-rate attainable with $^{198}$Au, removable implants of this material are more effective against the faster-growing malignant tumors.

Another radionuclide, iodine-125 ($^{125}$I), is now being tested against brain tumors. The radioactivity of $^{125}$I is high; but because its gamma emission is less energetic by a factor of 10 than that of $^{198}$Au or $^{192}$Ir, its radiation field is concentrated within a radius of 2.5 cm or less. This low-energy gamma emission also makes it easier to protect medical personnel and the patients' families against the nuclide when $^{125}$I is used.

Key Words • brachytherapy • brain tumor • iridium-192 • gold-198 • iodine-125 • radionuclide • radiation therapy

The efficacy of conventional external radiation (teletherapy) for the treatment of primary brain tumors is well established.\textsuperscript{13,18,20} The major limitation of teletherapy derives from the relative intolerance of normal tissues to radiation, making the delivery of potentially curative doses impossible. Brachytherapy by permanent or removable radionuclide implants, which confine the radiation to the tumor area, has been used in many body sites with good results in terms of both increased longevity and palliation.\textsuperscript{6} Brachytherapy has not, however, been routinely employed for brain tumors,\textsuperscript{8} although the use of permanent interstitial implantation of radionuclide seeds (gold, iridium, and yttrium) for both slow-growing and malignant gliomas has been pioneered by Mundinger, \textit{et al.},\textsuperscript{11-14} and by Talairach, \textit{et al.}\textsuperscript{18}

During the last 3 years, we have used stereotaxically implanted radionuclide seeds, either permanent or removable, to treat 10 patients with primary brain tumors. Seven of the 10 were treated for tumor recurrence after previous chemotherapy and/or radiation teletherapy. The response of these irremediable lesions was sufficiently encouraging that we are reviewing the biophysics of low-dose radiation in brain tumors. Our technique of surgical implantation of the radioactive seeds and the results achieved with brachytherapy are the subject of this preliminary report.

Materials and Methods

Ten patients harboring gliomas of various degrees of malignancy were selected for brachytherapy. The histories and clinical courses of these patients are summarized in Table 1. Seven of them harbored tumors that had recurred after treatment by surgery, whole-brain radiation, and all feasible chemotherapeutic agents (which in four cases had to be discontinued be-
### TABLE 1
Summary of the clinical courses of 10 patients treated with interstitial brachytherapy for brain tumors

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Date Tumor Diagnosed</th>
<th>Initial Tumor Histology</th>
<th>Prior Treatment</th>
<th>Date of Implant</th>
<th>Radio-nuclide</th>
<th>Dose (rads)</th>
<th>Survival after Implantation (mos)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57, M</td>
<td>Jan, 1977</td>
<td>astrocytoma*</td>
<td>none</td>
<td>Jan, 1977</td>
<td>$^{192}$Ir</td>
<td>10,500</td>
<td>22 (12 asymptomatic)</td>
<td>recurrence due to disseminated tumor seeding</td>
</tr>
<tr>
<td>2</td>
<td>51, M</td>
<td>Dec, 1976</td>
<td>malignant astrocytoma</td>
<td>surgery, irradiation (6000 rads), chemotherapy</td>
<td>Mar, 1977</td>
<td>$^{192}$Ir</td>
<td>10,000</td>
<td>2</td>
<td>died; autopsy, see text</td>
</tr>
<tr>
<td>3</td>
<td>53, M</td>
<td>Jan, 1969</td>
<td>astrocytoma</td>
<td>surgery, irradiation (3100 rads)</td>
<td>May, 1977</td>
<td>$^{192}$Ir</td>
<td>10,000</td>
<td>21 (18 stable)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>44, M</td>
<td>Jul, 1975</td>
<td>glioblastoma multiforme</td>
<td>surgery, irradiation (5900 rads), chemotherapy</td>
<td>May, 1977</td>
<td>$^{192}$Ir</td>
<td>10,000</td>
<td>4</td>
<td>died</td>
</tr>
<tr>
<td>5</td>
<td>43, M</td>
<td>Feb, 1976</td>
<td>mixed glioma</td>
<td>surgery, irradiation (5900 rads), chemotherapy</td>
<td>Jun, 1977</td>
<td>$^{192}$Ir</td>
<td>12,000</td>
<td>15 (11 stable)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>21, F</td>
<td>Aug, 1976</td>
<td>astrocytoma*</td>
<td>irradiation (5500 rads)</td>
<td>May, 1978</td>
<td>$^{192}$Ir</td>
<td>12,000</td>
<td>13 (8 stable)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>41, M</td>
<td>Sep, 1977</td>
<td>glioblastoma multiforme</td>
<td>irradiation (2000 rads)</td>
<td>Oct, 1977</td>
<td>$^{198}$Au</td>
<td>4000</td>
<td>1</td>
<td>died</td>
</tr>
<tr>
<td>8</td>
<td>57, M</td>
<td>Nov, 1976</td>
<td>malignant astrocytoma</td>
<td>surgery, irradiation (6000 rads), chemotherapy</td>
<td>Feb, 1978</td>
<td>$^{198}$Au</td>
<td>7350</td>
<td>22 &amp; continuing</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>49, F</td>
<td>Mar, 1979</td>
<td>astrocytoma</td>
<td>irradiation (5000 rads)</td>
<td>Aug, 1979</td>
<td>$^{198}$Au</td>
<td>4000</td>
<td>6 &amp; continuing</td>
<td>nuclide removed after 48 hrs</td>
</tr>
<tr>
<td>10</td>
<td>51, F</td>
<td>Oct, 1978</td>
<td>glioblastoma multiforme</td>
<td>surgery, irradiation (6000 rads), chemotherapy</td>
<td>Apr, 1979</td>
<td>$^{198}$Au</td>
<td>5500</td>
<td>9 &amp; continuing (5 asymptomatic; aphasic since recurrence)</td>
<td>nuclide removed after 76 hrs</td>
</tr>
</tbody>
</table>

*No initial biopsy; histology confirmed at time of implant.

cause of compromised marrow reserves). Two patients (Cases 3 and 7) had initially been treated with conventional whole-brain irradiation, and brachytherapy was subsequently employed for treatment of residual tumor. Brachytherapy was the primary treatment for one patient (Case 1), who harbored a large glioma in the pineal region.

In eight cases, radionuclide seeds were implanted permanently. Iridium ($^{192}$Ir) seeds, with a half-life of 74.2 days, were used for less malignant, slow-growing tumors, and gold ($^{198}$Au) seeds, with a half-life of 2.7 days, for fast-growing malignant tumors. In two cases (Cases 9 and 10), a $^{198}$Au seed with a higher radiation dose was encased in plastic tubing and implanted in the core of the tumor for 2 or 4 days, then removed.

Implantation was accomplished stereotaxically in two separate procedures, each under local anesthesia and employing Leksell stereotaxic apparatus.* In the first operation, a burr hole was made in a paramedian location on the vertex, and tumor biopsy was performed with a No. 17 needle. For fear of intratumoral hemorrhage, no persistent effort was made to obtain a conclusive specimen if a single trial did not provide one; and biopsy was therefore confirmatory in only three of the 10 cases. Immediately after the biopsy, a nonradioactive (dummy) seed of copper (22 gauge, 2 mm long) was delivered to the center of the tumor, using a preoperative computerized tomography (CT) scan as a guide. A localizing CT scan was then obtained to relate the dummy seed to the true tumor center. The artifact produced by the seed in CT scans was minimized by using copper for the dummy. In a second operation several days later, the radionuclide seed was placed precisely in the center of the tumor, using the dummy as a reference.

Radiation dosimetry was calculated on the basis of tumor shape as indicated by CT scan. All 10 of the tumors were round or ovoid and were less than 6 cm in diameter. Six patients (Cases 1–6) were irradiated with $^{192}$Ir in a total dose of 10,000 to 12,000 rads delivered to the periphery of the tumor; Cases 7

*Leksell stereotaxic apparatus manufactured by Downs Surgical, Inc., 2500 Park Central Boulevard, Decatur, Georgia.
Radionuclide therapy of brain tumors

Fig. 1. Case 10. Computerized tomography (CT) scans (axial) showing a glioblastoma multiforme that recurred in the left frontal lobe of a 50-year-old woman. The tumor is shown before (A) and after (B) stereotaxic implantation of $^{198}$Au, by which an additional 5500 rads was delivered. The patient's hemiparesis and dysphasia improved markedly for 5 months, but an axial CT scan made 5 months after brachytherapy (C) shows the recurrent left frontal glioblastoma.

and 8 were treated with permanent $^{198}$Au implants that delivered doses of 4000 and 7350 rads, respectively; and Cases 9 and 10 received, respectively, 4000 and 5000 rads, delivered by a removable $^{198}$Au implant.

The patients were re-evaluated at 8-week intervals by neurological examination and CT scan and, except for the patients with $^{192}$Ir implants, radionuclide scan. On the basis of these criteria, patients were assigned grades according to a system described previously. A response was defined as a definite improvement indicated by at least two of the criteria while steroid dosages were stable or decreasing; progression was defined as deterioration indicated by at least two criteria while steroid dosages were stable or increasing; stable disease was defined as no definite change indicated by more than one of the criteria. Grades for the patients who did not have radionuclide scans because they received $^{192}$Ir seeds (which give off gamma radiation that the camera could not filter) were determined on the basis of the other two criteria only. Patients were evaluated if they were alive and available for their first re-evaluation at 8 weeks after implantation of the radioactive seed. Time to tumor progression was measured from the day of implantation of the radioactive seed until the time that progression was documented by the aforementioned criteria.

Results

The overall results are presented in Table 1. There was a surgical complication in only one case: a wound infection at the site of the burr hole. Three patients (Cases 2, 4, and 7) died within 4 months of nuclide implantation. Autopsy was not performed on Cases 4 and 7; postmortem examination of Case 2 showed total necrosis of the tumor with no effect of radiation on surrounding normal brain tissue. It appeared that

and the patient died as a result of tumor expansion due to necrosis produced by irradiation.

Four of six patients responded to brachytherapy by $^{192}$Ir with tumor regression accompanied by improvement of their neurological deficits, or with an interval without progression of from 8 to 18 months (Case 6: 8 months; Case 5: 11 months; Case 1: 12 months; Case 3: 18 months). Three of four patients responded to irradiation with $^{198}$Au: Case 8 has remained free of progression for 24 months; another patient (Case 9) survived for 6 months without evidence of recurrence on either CT or radionuclide scans; and the third (Case 10) showed a remarkable initial response: her large recurrent anaplastic glioma of the left frontal lobe almost completely melted (Fig. 1A and B), and her neurological symptoms (aphasia and right hemiparesis) completely cleared. Four months later, however, the lesion began to recur (Fig. 1C).

Discussion

For the present, a two-stage procedure for implantation of the seed is necessary in order to achieve accurate placement of the radionuclide. The need for a second operation would, however, be obviated by the recently developed concept of a stereotaxic frame that fits into the CT scanner. This frame would allow more accurate placement of isotopes and thus more precise calculation of dosimetry; it would eliminate the need to plant a dummy seed to guide placement of the actual radionuclide. Our paramedian approach avoids the use of cumbersome intraoperative angiography that the lateral approach requires.

In teletherapy, the dose rate is one of the main factors determining the tumor cell kill: as the dose rate is lowered, the effect of a given dose of ionizing radiation is reduced because of the ongoing repair of sublethally
damaged cells. Furthermore, if the dose rate falls low enough, the irradiated cells will again begin to undergo mitosis. These two factors (together called the dose-rate effect) can dramatically reduce the slope of the survival curve.1

In contrast to teletherapy, in which a burst of, typically, 150 to 200 rads/min (9000 to 12,000 rads/hr) is delivered daily, the radioactive implants used in brachytherapy irradiate the tumor and a limited volume of surrounding normal tissue at a continuous dose rate of 10 to 100 rads/hr. With brachytherapy, the dose-rate effect is lessened: the low dose rate allows cells to continue to undergo oxygenation, which increases their radiosensitivity and thus serves to cancel out the effect of ongoing repair of the sublethal damage that occurs at low dose rates.6,10 In addition, the radiation delivered to normal tissues is greatly reduced, because the exposure level decreases by the inverse square of the distance from the radiation source.3,7,17 This capacity of implanted seeds to localize radiation and confine its effects mainly to tumor cells affords a rate of cell kill for brachytherapy that is far higher than that of conventional multifractionated teletherapy.5,10

Theoretical advantages have been postulated for low-dose irradiation from sources having long half-lives;18 but, as is apparent from Case 4, a higher dose rate may be necessary to control a faster-growing tumor. Therefore, 198Au, with its short half-life (2.7 days), seems to us to be the superior nuclide for brachytherapy of more rapidly growing tumors, such as glioblastoma multiforme and anaplastic astrocytoma. Since 198Au emits gamma rays of high energy, the seed must be implanted temporarily and removed after a few days in order to avoid protracted radiation of normal tissues and public hazard of radiation at low dose rates.19,20 It now appears that the radionuclide best suited to brachytherapy of brain tumors may be iodine-125 (125I), with a half-life of 60.2 days. It has high radioactivity, but because its gamma emission is less energetic by a factor of 10 than that of 198Au or 192Ir, its radiation field is concentrated within a radius of 2.5 cm or less. The low-energy gamma emission of 125I also makes it easier to protect medical personnel and patients' families when this nuclide is used. Iodine-125 with a higher specific activity (40 mCi), and therefore a higher dose-rate, first became available to us in November, 1979, and we plan to use this for our next series of removable implants in rapidly growing tumors.

Despite the number of good initial responses by these patients with hopeless recurrent tumors, our efforts failed in all but two. Obviously, the recurrence of tumor following brachytherapy is partly due to inadequate irradiation of the tumor cells, especially around the periphery of the tumor, where the dose rate is already significantly diminished.5 Moreover, it recently became apparent that the image of a tumor obtained by CT scan represents only 80% of the actual tumor: the serial biopsy made when the radioactive seed was implanted showed that the tumor cells extend usually 5 to 10 mm beyond the tumor area seen on the CT scan.10 Similar findings were reported in a study correlating CT scans with autopsy findings.16 We failed to take these peripheral tumor cells into account when dosimetry was calculated. Thus, it is clear that the success of brachytherapy of brain tumors depends on exact outlining of the tumor and exact definition of its volume. Even with a temporarily implanted 198Au seed, however, the emission of high-energy gamma rays makes it impossible to irradiate such a wide tumor area without affecting normal tissue.

It now appears that the radionuclide best suited to brachytherapy of brain tumors may be iodine-125 (125I), with a half-life of 60.2 days. It has high radioactivity, but because its gamma emission is less energetic by a factor of 10 than that of 198Au or 192Ir, its radiation field is concentrated within a radius of 2.5 cm or less. The low-energy gamma emission of 125I also makes it easier to protect medical personnel and patients' families when this nuclide is used. Iodine-125 with a higher specific activity (40 mCi), and therefore a higher dose-rate, first became available to us in November, 1979, and we plan to use this for our next series of removable implants in rapidly growing tumors.

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