Interstitial hyperthermia and iridium brachytherapy in treatment of malignant glioma

A Phase I clinical trial

DAVID W. ROBERTS, M.D., CHRISTOPHER T. COUGHLIN, M.D., TERENCE Z. WONG, M.S., JONATHAN D. FRATKIN, M.D., EVAN B. DOUPLE, PH.D., AND JOHN W. STROHBEHN, PH.D.

Division of Neurosurgery, Department of Surgery, and Division of Radiation Therapy, Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, and Thayer School of Engineering, Dartmouth College, Hanover, New Hampshire

An oncolytic effect of hyperthermia in the 42° to 43°C range has been previously demonstrated in cell culture and animal models. To apply this modality clinically, an interstitial microwave antenna array system has been developed for the delivery of controlled hyperthermia to an intracranial tumor volume, and a Phase I clinical trial involving six patients with malignant gliomas was undertaken. The protocol to study technical feasibility and patient tolerance combined interstitial iridium-192 irradiation and interstitial hyperthermia with 60-minute hyperthermia sessions immediately before and after brachytherapy. After-loading catheters suitable for both treatment modalities were implanted using a computerized tomography-assisted technique. Thermometry data confirmed the ability of a microwave antenna system to achieve reliable temperature distributions, and reasonable patient tolerance was documented.

KEY WORDS: astrocytoma • glioblastoma multiforme • hyperthermia • radiation therapy • stereotaxic procedure

The application of heat in the treatment of tumors has been employed for centuries, and in the last decade substantial biological data have been accumulated documenting the oncolytic effect of such treatment.15,23,26,28 The effectiveness of hyperthermia against hypoxic and poorly vascularized tissue, its lack of notable toxicity, and its ability to potentiate significantly both radiation therapy1,8,17,18,20 and chemotherapy1,15,16,24,38 have generated interest in the modality. The rationale for using hyperthermia on brain tumors has been reviewed,28 and a few clinical cases were reported as early as 1971.35

For a number of years the Dartmouth-Hitchcock Medical Center, in collaboration with the Thayer School of Engineering at Dartmouth College, has been developing an interstitial microwave antenna array hyperthermia system,6,7,11,32-34,39 based on small linear coaxial microwave dipole antennas.9,19,36,37 Clinical trials of this method for treatment of superficial, abdominal, pelvic, and other malignancies have been instituted. Our experience with a Phase I clinical trial of interstitial microwave-induced hyperthermia in conjunction with iridium-192 (192Ir) brachytherapy for malignant glioma is presented in this report. Our objective was to assess the feasibility of this hyperthermia technique and the tolerance of such treatment by the patient.

Clinical Material and Methods

Patient Selection

Criteria for inclusion in this study were: histological confirmation of the diagnosis of malignant glioma (grade III or IV); a tumor location that precluded attempted surgical resection (or refusal by the patient to undergo surgical resection); and appropriate informed consent including formal acceptance of the investigational consent form, as approved by the institution's Human Experimentation Committee. From April 1, 1983, to September 1, 1984, a total of six patients fulfilled these criteria and were entered into this study. A seventh patient with a significantly larger glioblastoma multiforme was also entered into the study but, following
biopsy and interstitial catheter implantation, she deteriorated clinically and was not treated.

Interstitial Microwave Hyperthermia System

The interstitial microwave antenna array hyperthermia system used in this study has been described previously. The system is summarized in Fig. 1. It has a Holaday HI-915 microwave power source* that generates 0 to 300 W at 915 MHz; microwave antennas, constructed from RG178B/U coaxial cable (without jacket) and after-loaded into stereotaxically implanted nylon catheters of 2.2-mm outer diameter, deliver that power. Thermometry was performed in these six patients using thermistors or fiberoptic probes both on the antennas and along a catheter implanted perpendicular to the antenna array.

Operative Technique

Stereotaxic placement of the catheter array was accomplished using the Leksell computerized tomography (CT)-adapted stereotaxic system.† A tentative geometric array dictated by dosimetric and anatomical constraints was determined from the patient's presenting CT scan, and the actual stereotaxic coordinates for the catheter implantation were generated on a General Electric 8800 scanner with the Leksell frame on the patient. Catheter array and location were determined for these six patients by visual superimposition of a grid template over the CT-demonstrated tumor, such that its contrast-enhancing margin and a surrounding 5-mm periphery lay within that field on appropriate axial slices. A computerized dosimetry system is currently under development. Radiation dosimetry was calculated by conventional orthogonal plain-film techniques and a treatment-planning software program.

Catheter placement was performed under local anesthesia through 5-mm skin incisions and craniotomies made with a 3-in. Steinmann pin driven by an air-powered drill through the stereotaxic guide. The dura was coagulated and perforated by an insulated needle with electrocautery, and the catheter was then placed through the stereotaxic guide. A central stylette was withdrawn and the catheter secured by cyanoacrylate glue to a button sutured to the scalp.

Parallel arrays of four, five, or six catheters were employed. An additional catheter was placed in order to measure temperatures within the tumor volume and at the tumor margin; this catheter was oriented perpendicular to the active array to minimize perturbation effects from the microwave field. The recent addition of a radiofrequency transparent fiberoptic thermometry system‡ has eliminated the restriction on the orientation of the thermometry catheter. At the time of catheter placement, a Silastic ventricular catheter was placed stereotaxically and tunneled subcutaneously for the purpose of monitoring intracranial pressure (ICP). For the two most recent patients, temperature and ICP data were recorded automatically by a Hewlett-Packard 87 computer. Temperatures were measured at each antenna, and power to each antenna was controlled through the computer to maintain desired temperatures.

Treatment Protocol

The day following biopsy and catheter placement, the microwave antennas were inserted into the catheters and heating was begun with the objective of inducing a temperature of 42° to 43°C at the tumor periphery for 60 minutes. Throughout the hyperthermia treatment, the unanesthetized patient was monitored by neurologic examination, ICP measurement, electroencephalography, and visual evoked responses. The antennas and thermometry probes were then removed and ribs of 0.55- to 1.0-mCi 192Ir seeds were inserted into the same catheters, with dosimetry calculated to deliver approximately 20 Gy to the tumor periphery over 3 to 9 days. A second hyperthermia treatment was then performed with parameters similar to the first treatment, the catheters were removed, and the skin incisions were sutured under local anesthesia. The ICP was monitored for an additional 24 to 48 hours, and the patient was discharged from the hospital soon afterward. One week later, the patient returned as an outpatient for conventional external-beam irradiation carried to 60 Gy over 6 weeks using a shrinking field technique.

Patient Evaluation

Outpatient follow-up review assessed the clinical course weekly until the completion of radiation therapy, then monthly for the next 2 months, and every 2

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* Holaday HI-915 microwave power source manufactured by Holaday Industries, Eden Prairie, Minnesota.
† Leksell stereotaxic system manufactured by Downs Surgical, Inc., Decatur, Georgia.
‡ Radiofrequency transparent fiberoptic thermometry system, Model 1200, manufactured by Clini-Therm Corp., Dallas, Texas.
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<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Tumor Location</th>
<th>Previous Treatment</th>
<th>Microwave Antenna Array†</th>
<th>Boundary Temp. (°C)</th>
<th>Maximum Temp. (°C)</th>
<th>Radiation Dose (Gy)</th>
<th>Complications</th>
<th>Survival Time Post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>rt frontoparietal</td>
<td>none</td>
<td>4 (2 cm, square)</td>
<td>39</td>
<td>46</td>
<td>18.95</td>
<td>50 + 10 increased paresis, transient</td>
<td>16 mos, dead</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>lt parietal</td>
<td>none</td>
<td>4 (2 cm, square)</td>
<td>39-41.5</td>
<td>46</td>
<td>21.2</td>
<td>44 increased paresis, transient</td>
<td>1.5 mos, dead (MI)</td>
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<tr>
<td>3</td>
<td>48</td>
<td>lt frontal</td>
<td>partial resection, irradiation</td>
<td>6 (2 × 4 cm, rectangle)</td>
<td>41-43</td>
<td>52+</td>
<td>21.51</td>
<td>0 CSF leak; meningitis, recovered</td>
<td>13 mos, dead</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>rt frontal</td>
<td>none</td>
<td>5 (2 cm, square + central)</td>
<td>39</td>
<td>39-40</td>
<td>20.1</td>
<td>50 + 10 increased paresis</td>
<td>5 mos, dead</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>rt frontal</td>
<td>partial resection</td>
<td>5 (2 cm, square + central)</td>
<td>42-43</td>
<td>46</td>
<td>17.5</td>
<td>50 + 10 none</td>
<td>12 mos, dead</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>lttemporoparietal</td>
<td>partial resection × 2, irradiation × 2</td>
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<td>40-41.5</td>
<td>47</td>
<td>65.8</td>
<td>0 increased paresis, transient</td>
<td>10 mos, alive</td>
</tr>
</tbody>
</table>

* CSF = cerebrospinal fluid; MI = myocardial infarction.
† Numbers of catheters in each array.

months thereafter. A CT scan was obtained prior to discharge from the hospital, at 1 month, and then every 2 to 4 months.

**Results**

**Summary of Cases**

Clinical treatment data for the six patients in this study are summarized in Table 1. Three men and three women, ages 35 to 73 years (mean 55.3 years), underwent catheter placement and treatment. Tumors were located in the right frontal area (two), left frontal area (one), left parietal area (one), left temporoparietal area (one), and right frontoparietal area (one). Three patients had undergone partial resection prior to entering this protocol, and two of these had previously had external-beam irradiation.

Four-catheter arrays, 2-cm square, were employed for antenna placement in five patients, three of whom had an additional central catheter for improved hyperthermia and radiation dosimetry as well as more complete thermometry. One patient, with a larger recurrent tumor, had a six-catheter rectangular array. All patients tolerated the stereotaxic procedure well and underwent hyperthermia treatment the following day.

Mild and transient worsening of pretreatment neurological deficits was noted in three patients (Cases 1, 2, and 5) either during or immediately after hyperthermia treatment. One patient (Case 4) developed significant worsening of left arm weakness within minutes of beginning heat treatment, with rapid recovery upon cooling, and repeated intolerance of heating precluded further hyperthermia treatment in this patient. The 192Ir seeds were in place for between 66 and 212 hours, and the second hyperthermia treatment immediately follow-

ing seed removal was performed uneventfully, with the exception of Case 4, discussed above.

All patients were discharged home, and the four who had not received prior radiation therapy underwent treatment on an outpatient basis. One patient (Case 3) was admitted to the urology service 1 week following discharge with a ureteral calculus; during that hospitalization, he developed leakage of cerebrospinal fluid from an incision in his previously irradiated scalp. Subsequent coagulase-negative staphylococcal meningitis responded to appropriate antibiotic therapy; however, the patient and his family declined treatment of CT-demonstrated ventriculomegaly. One patient (Case 2) suffered a massive myocardial infarction during the course of his external-beam irradiation and died.

In the majority of patients, CT scanning after treatment showed early decreased enhancement of the tumor and increased surrounding edema (Fig. 2). In one patient (Case 3), a significant decrease in tumor size was noted (Fig. 3). Four patients died 5, 12, 35, and 16 months following completion of their interstitial treatment (6, 12, 35, and 16 months, respectively, after the diagnosis of their tumor). One patient is alive and neurologically stable 10 months after treatment.

**Thermometry Data**

No technical difficulties were encountered during thermometry recording, and the thermal profiles attained were similar to theoretical predictions. As noted, one patient did not tolerate even modest temperature elevation (maximum of 39° to 40°C), and in another patient scalp discomfort precluded full protocol heating during initial treatment. In five patients, heating of the central region of the tumor to greater than 43°C was achieved without difficulty. Reaching the desired
temperature at the periphery of the tumor was more
difficult, and was consistently achieved in only two
patients. Figure 4 illustrates the thermal profile achieved
in Case 3.

In general, power requirements for the second treat-
ment in a given patient were lower than those of the
first. In Case 3, for example, the first treatment required
10 W/antenna, while the second required only 6.3 W/
antenna. Theoretically, such differences are accounted
for by variation in blood perfusion (less power is re-
quired when blood flow is lower).

Patient Tolerance of Hyperthermia

All heat treatments were performed on unmedicated
alert patients and, with the exception of one treatment
in a patient who experienced transient local scalp heat-
ing at one catheter site, there was no discomfort or
pain. One other patient described a not unpleasant
sensation of deep warmth. Two patients experienced
transient unpleasant smells or tastes in their mouths.
There was no evidence of seizure activity.

Intracranial pressure was monitored throughout
treatment in all patients. In five patients, baseline ICP
remained unchanged during the period of measure-
ment, which included both hyperthermia treatments,
the interval between these treatments, and (in all but
one patient) extended 24 to 48 hours after treatment.
One patient (Case 3) had an increase in ICP from 10
cm H\textsubscript{2}O prior to treatment and during the first 45
minutes of initial heating to an asymptomatic peak of
40 cm H\textsubscript{2}O at 55 minutes of his treatment. Return to
baseline ICP followed cessation of his hyperthermia
treatment. During his second hyperthermia treatment,
ICP rose from a baseline of 4 cm H\textsubscript{2}O to a maximum
of 21 cm H\textsubscript{2}O at 35 minutes. This returned to baseline
by the completion of that treatment session.

Electroencephalographic recordings during heating
demonstrated improvement in delta wave activity over
the hemisphere of tumor involvement in two patients
(Cases 1 and 2). In addition, there was a general im-
provement in faster background frequencies. No clear
epileptiform activity was evident during heating.
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Fig. 4. Temperature distribution during hyperthermia treatment (Tx) in Case 3. The medial margin of tumor (distance = 0) was maintained at 42° to 43°C after the warm-up period. The left lateral tumor margin was estimated to be at 55 mm.

Visual evoked response testing was performed during hyperthermia treatment in two patients (Cases 1 and 2). In both instances there was an initially increased latency on the side of tumor involvement and, not unexpectedly, this improved significantly during the period of temperature elevation. Latencies returned to pretreatment values immediately upon cooling. There was no subjective change in any patient's vision during hyperthermia treatment.

Pathology

A postmortem investigation of Case 2 demonstrated central necrosis, shown on the gross specimen in Fig. 5. Microscopic study of this section revealed a well demarcated transition zone between this necrosis and surrounding viable tissue (Fig. 6). This histology was correlated with available temperature data and thermal dose (equivalent minutes at 43°C). Coagulation necrosis was evident in the central region where the thermal dose exceeded 100 equivalent minutes at 43°C, and viable tissue was found at the periphery where the thermal dose was less than 20 equivalent minutes. These findings, similar to those found in animal models, are consistent with a hyperthermia effect. Edema, noted on CT scans and reported in animal studies, was present but not marked.

Discussion

The mechanism by which hyperthermia exerts its antineoplastic effect is not well understood. However, its effectiveness has been observed to extend to tumor regions characterized by hypoxia, low pH, and low growth fractions, all features generally associated with increased resistance to radiation and chemotherapy. This ability has stimulated interest in the modality as a possible adjunctive therapy in the treatment of malignant glioma.

Salcman and Samaras have reported their expe-
ience with a Phase I clinical trial of interstitial microwave hyperthermia for malignant glioma. Following partial resection of their recurrent tumor, six patients underwent placement of a single microwave (2450-MHz) antenna. They then received a limited intraoperative dose of hyperthermia and later two 60-minute treatments. Dosimetry relative to tumor margins was not clear, in view of their free-hand technique and rather limited thermometry, but clinical safety was established.

Thermometry data using the present system in clinical trials involving tumors of the pelvis, abdomen, chest wall, and soft tissue6,7 and in animal models52 have previously confirmed the predicted ability of a microwave antenna system to achieve desirable temperature distributions. Data from the present trial are limited by the number of thermometry points, but in general conform to earlier experience. Adoption of newer nonperturbed thermometry probes (which can share catheters used by active antennas) and computerized control of those probes for both positioning and analysis greatly expand the number of data points. Coupled with independent control of the power to each antenna, this development is greatly improving the described technique. Small thermal heterogeneities secondary to the microcirculation presumably account for the residual tumor that has been histologically observed by Overgaard and Nielsen26 and Britt and coworkers (data presented at the Radiation Research Society, 1984), but the clinical significance of this finding remains to be determined.

While a variety of unintended difficulties have arisen in a relatively small number of patients, the overall tolerance of this technique has been good. The most serious complication appears to be that of increased neurological deficits, but this is not surprising given the poor location and infiltrating nature of the tumors involved. Protection of normal brain may be benefited by a potential therapeutic window. Some workers have shown evidence that tumor cells may be more heat-sensitive than normal cells in the 42° to 43°C range,5,10,18,27 but there are conflicting studies.15 No information relating to brain cells exists on this point. Protection through manipulation of selective thermal tolerances is a provocative concept but at the present time largely speculative.

To the extent that catheter insertion contributes to the overall morbidity, it is appropriate to bear in mind the probably adjuvant rather than primary treatment role of hyperthermia. With the therapeutic enhancement ratio of hyperthermia on radiation therapy as high as 4.3:128 and with increasing evidence in support of using interstitial irradiation in brain-tumor therapy,13,14,25 an interstitial hyperthermia system can be employed in combination with interstitial irradiation using the same catheters with little additional risk. Radiation dosimetry constraints dictated by both theory and present data demand a closer catheter placement than is used in hyperthermia dosimetry; in our series, array geometry was designed primarily to satisfy the radiation requirements, and the hyperthermia system was adapted to comply. Noninvasive hyperthermia systems (such as ultrasound and magnetic concentric coils) have obvious advantages over invasive interstitial techniques, but there are major difficulties in their ability to achieve reliable homogeneity of heat deposition.31 In addition, thermometry measurement at present remains necessary and is invasive in itself.

Perhaps the greatest difficulty that must be addressed by any form of regional treatment is that of defining the volume to be treated. The imperfect correlation between CT morphology and actual histology is widely recognized.4 Other imaging techniques may help resolve this difficulty, but the troublesome glioma periphery will in all likelihood continue to plague the efficacy of any interstitial technique. Documented tumor progression in this series appeared to develop from the tumor periphery. Treatment failure presumably arose secondary to arbitrarily defined tumor peripheries not extending far enough and to subtherapeutic thermal doses delivered to that periphery. More aggressive treatment planning in terms of greater volume dosimetry and more sophisticated dosimetry calculation are expected to improve these results.

The theoretical benefit of hyperthermia application, especially in combination with interstitial irradiation and possibly chemotherapy, is sufficiently encouraging that further investigation is clearly indicated. This clinical trial has demonstrated technical feasibility and reasonable patient tolerance. Determination of the efficacy of such a technique awaits larger long-term clinical experience.

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References

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Address reprint requests to: David W. Roberts, M.D., Section of Neurosurgery, Dartmouth-Hitchcock Medical Center, Hanover, New Hampshire 03756.