Accelerated fractionated proton/photon irradiation to 90 cobalt gray equivalent for glioblastoma multiforme: results of a phase II prospective trial

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Object. After conventional doses of 55 to 65 Gy of fractionated irradiation, glioblastoma multiforme (GBM) usually recurs at its original location. This institutional phase II study was designed to assess whether dose escalation to 90 cobalt gray equivalent (CGE) with conformal protons and photons in accelerated fractionation would improve local tumor control and patient survival.

Methods. Twenty-three patients were enrolled in this study. Eligibility criteria included age between 18 and 70 years, Karnofsky Performance Scale score of greater than or equal to 70, residual tumor volume of less than 60 ml, and a supratentorial, unilateral tumor.

Actuarial survival rates at 2 and 3 years were 34% and 18%, respectively. The median survival time was 20 months, with four patients alive 22 to 60 months postdiagnosis. Analysis by Radiation Therapy Oncology Group prognostic criteria or Medical Research Council indices showed a 5- to 11-month increase in median survival time over those of comparable conventionally treated patients. All patients developed new areas of gadolinium enhancement during the follow-up period. Histological examination of tissues obtained at biopsy, resection, or autopsy was conducted in 15 of 23 patients. Radiation necrosis only was demonstrated in seven patients, and their survival was significantly longer than that of patients with recurrent tumor (p = 0.01). Tumor regrowth occurred most commonly in areas that received doses of 60 to 70 CGE or less; recurrent tumor was found in only one case in the 90-CGE volume.

Conclusions. A dose of 90 CGE in accelerated fractionation prevented central recurrence in almost all cases. The median survival time was extended to 20 months, likely as a result of central control. Tumors will usually recur in areas immediately peripheral to this 90-CGE volume, but attempts to extend local control by enlarging the central volume are likely to be limited by difficulties with radiation necrosis.

Keywords: • glioblastoma multiforme • dose escalation • radiation therapy • proton
TABLE 1
Tumor and radiotherapy characteristics in 23 patients treated with proton/photon irradiation for GBM*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>preop Gd T1 volume (ml)</td>
<td>33</td>
<td>3–99</td>
</tr>
<tr>
<td>preop Gd T2 diameter (cm)</td>
<td>4.5</td>
<td>2–7.5</td>
</tr>
<tr>
<td>postop Gd T1 residual volume (ml)</td>
<td>&lt;1</td>
<td>0–42</td>
</tr>
<tr>
<td>V1 volume (ml; 90 CGE)†</td>
<td>36</td>
<td>6–115</td>
</tr>
<tr>
<td>V2 volume (ml; 64.8 CGE)†</td>
<td>148</td>
<td>67–272</td>
</tr>
<tr>
<td>V3 volume (ml; 50.4 CGE)†</td>
<td>337</td>
<td>126–563</td>
</tr>
<tr>
<td>time from surgery to RT (days)</td>
<td>36</td>
<td>21–85</td>
</tr>
<tr>
<td>treatment time of RT (days)</td>
<td>37</td>
<td>31–45</td>
</tr>
<tr>
<td>total dose (CGE)‡</td>
<td>93.5</td>
<td>81.6–94.2</td>
</tr>
<tr>
<td>proton dose (Gy)‡</td>
<td>52.4</td>
<td>29.7–62.9</td>
</tr>
</tbody>
</table>

* Gd = gadolinium-enhanced; RT = radiotherapy; T1 = T1-weighted MR image.
† Proton dose expressed in gray is multiplied by a factor of 1.1 (to account for relative biological effectiveness) to calculate the dose in CGE. Added to this is the dose given with x-irradiation. The doses given in the table represent the recalculated doses after the calibration change in proton-dose determination (see text).

Clinical Material and Methods

Patient Population

All patients were assessed and followed by the Massachusetts General Hospital (MGH) Neuro-oncology Group. The protocol was open between 1992 and 1996, and 23 patients selected for the study underwent radiotherapy following resection of a GBM. Pathological specimens were evaluated by a neuropathologist at MGH (E.T.H.W.). Eligibility criteria were as follows: 1) patient age between 18 and 70 years; 2) pathologically proven Grade IV/V astrocytoma according to the classification of Daumas-Duport, et al.; 3) Karnofsky Performance Scale (KPS) ≥ 70 score of 70 or higher prior to radiotherapy; 4) previously attempted maximal surgical resection; 5) largest postoperative tumor volume less than 60 ml (approximately equal to the largest postoperative diameter of 5 cm); and 6) supratentorial primary tumor with no involvement of the thalamus, corpus callosum, or subependyma. Exclusion criteria were as follows: 1) prior radiotherapy to the head and neck, except for skin carcinomas; 2) genetic syndrome linked to central nervous system malignancies; 3) known radiation hypersensitivity syndrome; 4) collagen vascular disease; 5) diabetes mellitus; and 6) serious concomitant disease precluding completion of the protocol.

Radiotherapy Protocol

Three-dimensional (3-D) CT-based treatment planning was used for each patient. The planning system has been described previously. A contrast-enhanced CT scan with 3-mm slice thickness was obtained while the patient’s head was placed in the appropriate immobilization device developed for treatments at the Harvard Cyclotron Laboratory. An MR image was obtained, taking care to reproduce in its axial reconstruction the transverse plane of the planning CT scan as closely as possible. In addition, a functional (f)MR image (cerebral blood volume mapping) and a positron emission tomography (PET) scan with [18F]fluorodeoxyglucose were performed. The treatment volumes were then delineated on the CT planning scan with the aid of the MR, fMR, and PET study data, drawing the largest abnormality seen on these studies. Three clinical target volumes were defined: 1) the gross tumor volume (V1), encompassing the signal-intense rim of the tumor or the remaining cavity on the earliest postoperative study plus any residual gadolinium-enhancing volume on T2-weighted MR imaging; 2) a second volume at high risk for harboring dense microscopic disease (V2), comprising V1 plus a margin of 2 cm; and 3) a third volume at risk of less dense microscopic disease (V3), enclosing the edema volume as seen on T2-weighted MR imaging plus a margin of 2 cm. Prescriptions for V2 and V3 were similar to those used in most conventional treatment plans, except for the accelerated fractionation pattern. All three volumes were defined, taking into account the presence of natural anatomical barriers, such as bone structures, falx, and tentorium. Graded doses were prescribed for these volumes as follows: V1, 90 CGE; V2, 64.8 CGE; and V3, 50.4 CGE (proton grays were multiplied by 1.1 to account for relative biological effectiveness of the 160-MeV proton beam compared with cobalt gamma rays plus the dose delivered with x-irradiation). The protocol specified that patients receive 1.8 CGE per fraction with 10 fractions given per week, two fractions per day, with a minimum inter-fraction interval of 7 hours. The amount administered with protons as a fraction of the total dose was variable but not less than 33% of the total.

The median proton dose delivered was 52.4 Gy (57.6 CGE) with a range of 29.7 to 62.9 Gy (32.7–69.2 CGE). A dose calibration change was adopted at our institution 1 year after the last patient had been treated according to this protocol. That change was made after we recognized that the dose determined using an ion-chamber technique was 6.5% higher than that determined using the Faraday-cup technique, which had traditionally been used at the Harvard Cyclotron Laboratory. This resulted in a daily fraction size of 1.8 Gy with x-ray treatment and 1.92 CGE with protons, according to the ion-chamber technique. Thus, given the variable proportion of proton dose per patient, total doses differed slightly. In no instance did this exceed a 5% deviation from the stated protocol dose. No difference dependent on the proton-dose component was observed in the outcome measures presented later in this study. The final dose was lowered by 10% in one patient, to 81.6 CGE, because of the increasing concern of this individual about potential long-term side effects. The median total dose in the remaining 22 patients was 93.5 CGE with a range of 92.05 to 94.2 CGE. In the analysis of individual patients, the revised doses are stated. In the analysis of groups of patients and the design of target volumes, the dose estimated using the traditional Faraday-cup technique is applied for reasons of simplicity.
The median number of proton fields per patient was four (range two–seven). For each field, an individual aperture and depth compensator were manufactured, and a minimum of two fields were treated per day. The photon component was administered with 4-MV x-irradiation in 22 patients and with a 10-MV x-ray treatment in one. A median of three conformal x-ray fields (range two–four) were treated per patient; all x-ray fields received daily treatment. The median overall treatment time with radiotherapy was 37 days (range 31–45 days).

The relevant tumor and radiotherapeutic parameters are summarized in Table 1.

Patient Follow Up and Intervention at Imaging Change

The patients were evaluated 1 month after completion of radiotherapy and then at 3-month intervals or sooner, as clinically indicated. On each visit, physical and neurological examinations were performed, and an MR image was obtained. Functional imaging in the form of [18 F]fluorodeoxyglucose PET scanning or dynamic contrast-enhanced relative cerebral blood volume–mapping MR imaging was used to evaluate changes on routine MR studies. The appearance of new areas of gadolinium enhancement on posttreatment MR images prompted a recommendation for histological examination by stereotactically guided biopsy procedure or craniotomy. Radiation necrosis was treated with steroid drugs. If a resectable, symptomatic mass was present, reoperation was encouraged.15 Thirteen (57%) of 23 patients underwent either a biopsy (five patients) or resection (eight). Eight patients received various chemotherapy agents at the time of tumor progression, and five received only palliative care after recurrence.

Analysis of Imaging Studies

A total of 349 pre- and posttreatment MR and CT studies were reviewed by two radiation oncologists (M.F. and A.T.), two radiologists (J.R. and M.L.), and one neurosurgeon (G.H.). Tumor dimensions were measured with calipers on three axes: anterior–posterior, right–left, and superior–inferior. Volumes were calculated according to the formula for ellipsoids (\( V = \frac{4}{3} \pi abc \), where a, b, and c are the half-lengths of the three axes). The initial gross tumor volume was defined as the gadolinium-enhancing tissue on T1-weighted MR images, and the edema volume was defined as the signal-intense volume on T2-weighted images. The residual gross tumor volume was defined as the volume of gadolinium enhancement on the earliest postoperative image (obtained within 72 hours of surgery in 12 of 23 patients). The clinical target volume was calculated using a 3-D treatment planning system. This volume differed from the postoperative residual volume and the edema volume as measured by the caliper method because a different method of measurement was used, and the clinical target volumes included any surgical cavity present, as well as the signal-intense rim. Thin rims of contrast enhancement, often bright on noncontrast T1-weighted MR imaging, were attributed to postsurgical change by measurement with the caliper method and were not considered to be residual tumor.2 The first posttreatment image revealing an increase in the volume of gadolinium enhancement was compared with the 3-D CT-based treatment plan. The isodoses bracketing the area of the change were recorded as highest (closer to the center of the original tumor) and lowest isodose (closer to the periphery) of change. Radiographically determined distinction between tumor progression and radiation necrosis was frequently impossible. Therefore, we have preferred the term “imaging change” to the more conventional ones of “progressive disease” or “failure.” Figure 1 shows an example of imaging comparisons in one patient.

Statistical Analysis

Kaplan–Meier curves were calculated with the aid of the Stata program (version 5.0, Stata Corp., College Station, TX). The probability values that might identify data trends are shown on some curves even though they are greater than 0.05.

Results

Patient Group

Twenty-three patients (seven women and 16 men) were enrolled in the protocol, and none of them was lost to follow up. Their median age was 51 years, with a range of 21 to 68 years. Four patients presented with seizures only; in an additional five patients, seizures were a component of their presentation. The median symptom duration until diagnosis was 4 weeks, with a range of 1 day to 40 weeks. The median preradiotherapy KPS score was 90 (range 70–90). In 14 patients, the KPS score rose by 10 to 20 points postsurgery. Seven patients met Radiation Therapy Oncology Group (RTOG) prognostic Class III, seven met prognostic Class IV, and nine met prognostic Class V criteria. The median Medical Research Council (MRC) prognostic index, as described in Bleehen and Stenning,4 was 15 (range 5–30). Fourteen tumors were located in the dominant hemisphere. In all, five tumors originated from the frontal, eight from the parietal, two from the occipital, and four from the temporal lobe. Three tumors involved the parietal and occipital areas in approximately equal proportions, and one involved the frontal and parietal region. Comorbidity and medical histories for these patients were within the normal range for a generally healthy population of comparable age. Chemotherapy was not part of the initial management strategy, although it was not formally excluded: one patient received one course of procarbazine, carboplatin, and vincristine 6 weeks postoperatively while awaiting radiotherapy.

Surgical Treatment

Nineteen patients underwent initial surgery at MGH; four underwent operation at other institutions and were judged to be unlikely to benefit from further resection. One patient underwent a second operation before radiation treatment because of a previous incomplete resection. Nine resections were classified by the surgeon as gross total and 13 as subtotal; one patient underwent a biopsy procedure only. According to imaging criteria, 10 patients showed no residual gadolinium enhancement on T1-weighted MR studies, eight had residual volumes ranging from 0.1 to 1 ml, and five had volumes of more than 5 ml (range 5–42 ml). The median preoperative tumor volume as measured by the caliper method was 33 ml (range 3–99
Fig. 1. Neuroimaging studies obtained in a 57-year-old man who presented with a grand mal seizure and a 2-week history of subtle intellectual impairment. All studies are gadolinium-enhanced T1-weighted MR images except the radiation therapy—planning CT scan. **Upper Left:** Preoperative appearance of left temporal GBM. **Upper Right:** Postoperative appearance, subtotal resection. **Center Left:** Resolution of contrast enhancement 7 months postsurgery (4.5 months after completion of radiotherapy). **Center Right:** Appearance of first imaging changes 11 months postoperatively. The patient underwent subtotal resection of this area. Pathological examination revealed radiation necrosis only. **Lower Left:** The changes were visually correlated to the sections of the planning CT, and isodoses bracketing the change were recorded (in this scan the highest isodose was 90 CGE and the lowest isodose was approximately 85 CGE). Isodoses are displayed as CGE values. Outlines in black identify the three target volumes. Lines are enhanced to ease readability. **Lower Right:** Evidence of gradually progressive radiation necrosis on MR image obtained 28 months postsurgery. Patient is clinically stable 29 months after his first surgery with a KPS score of 50.
ml). The median largest preoperative tumor diameter on axial MR imaging in the anterior–posterior or right–left dimension was 4.5 cm (range 2–7.5 cm). The median interval from surgery to the start of radiotherapy was 36 days (range 21–85 days).

**Pathological Findings**

All tumors met the criteria of Daumas-Duport, et al., for Grade IV/IV astrocytoma. In addition, two tumors exhibited an oligodendrocytic component, one had features of an ependymoma, one had gliosarcomatous elements, and one was a giant cell glioblastoma.

**Treatment Tolerance (≤ 3 Months After First Radiation Treatment)**

The treatment was generally well tolerated. One patient required a break of 1 week (Day 19–26) after delivery of 41.4 CGE because of worsening cerebral edema and imminent herniation. Treatment with steroid agents and mannitol permitted completion of radiotherapy, but decompressive surgery was required 3 weeks later. Pathological examination of tissue from this and two subsequent resections showed only radiation necrosis. New symptoms that occurred during radiotherapy were nausea (eight patients), dizziness (two), headache (two), and blurred vision (one). These symptoms were adequately controlled using standard antiemetic medication and/or by an increase in the dose of steroid drugs. No patient who was initially free of steroids required initiation of these drugs during treatment. In four patients we were able to reduce the steroid dose during radiotherapy, whereas three patients required an increase in dose. The remaining seven patients were maintained on their initial levels of steroid medication. All of the 20 patients receiving anticonvulsant medications before radiation treatment continued to do so during therapy. Acute reactions were otherwise limited to skin erythema, desquamation, and alopecia. All surgical incisions were completely healed at the initiation of radiation treatment, and no wound dehisced or became inflected.

**Treatment Toxicity (> 3 Months After First Radiation Treatment)**

All but one patient required treatment with steroid drugs at the time of clinical deterioration. This occurred at a median time of 7.5 months after radiation therapy. Doses of steroid agents were adjusted frequently, and we found that aggressive tapering of the steroid dose consistently precipitated clinical deterioration. Of the four patients still alive, the one surviving for 60 months is the only one who did not require steroid medications after the postoperative period. All patients had areas of permanent alopecia. All patients in whom tissue was obtained for pathological assessment (described later) showed extensive radiation necrosis.

**Overall Survival and Quality of Survival**

The median survival time of the entire group of patients was 20 months after the first surgery and 18.6 months after beginning radiation therapy. The actuarial survival rates at 1, 2, and 3 years were 78%, 34%, and 18%, respectively, from the time of surgery. No patient died of intercurrent disease, and one died within the first 10.5 months after the initial surgery (Fig. 2 upper).

The median patient survival time while maintaining a KPS score of 70 or higher was 12 months. The actuarial rates for maintaining this high level at 1 and 2 years were 50% and 8%, respectively (data not shown). Two patients whose KPS score fell below 70 improved with treatment (high-dose steroid treatment in one and resection of necrosis in the other); a high level of function was subsequently maintained for 5 and 8 months, respectively. Four patients are currently alive at 22, 29, 37, and 60 months.
posttreatment. Two are working full-time, one as a computer programmer and the other as a housewife. The computer programmer (survival time 37 months) has been steroid-dependent for more than 2 years. He underwent resection of radiation necrosis at 11 and 21 months posttreatment. The housewife has not required steroid drugs since the early postoperative period and, at 60 months posttreatment, takes no medication. The other two surviving patients are steroid dependent. In one, a biopsy sample (from the 90-CGE volume) showed recurrent tumor 8 months after radiation therapy. He was retreated with stereotactically guided proton-beam radiosurgery (15 CGE protons) and 3.5 months later underwent resection of radiation necrosis. At 22 months after the initial treatment, he currently has a declining KPS score of 40. The other patient underwent resection of radiation necrosis 13 months after the start of radiotherapy. Although 29 months after the initial surgery his follow-up MR image now reveals slow progression of radiation necrosis, his KPS score is stable at 50. Three patients developed deep leg vein thrombosis; two underwent insertion of an inferior vena cava filter. Two patients required placement of a ventriculo-peritoneal shunt, and two developed significant steroid-induced diabetes mellitus.

Analysis of Prognostic Factors

To assess the influence of patient selection on outcome, individuals were grouped according to both RTOG and MRC prognostic criteria for malignant glioma.4,7 In the RTOG analysis, patients were divided into six prognostic classes: Class I had the best prognosis (younger patients with anaplastic astrocytoma) and Class VI had the worst (elderly patients with GBM and low KPS scores). Seven of our patients were Class III, seven were Class IV, and nine were Class V. The median survival time of Class III and IV patients combined was 20 months and that for Class V patients was 14 months (p = 0.07). Each patient was also assigned a prognostic index from the English MRC scheme, in which a lower score represents a more favorable prognosis. This scheme identifies groups of patients who have different probabilities of survival when uniform treatment is given. The MRC index scores of our patients ranged from 5 to 30 (median 15). The actuarial survival time for patients with an MRC prognostic index less than 15 was higher than for those with an index greater than 15 (24 and 16 months, respectively; p = 0.06) (Fig. 2). In univariate analysis, caliper-measured pre- or postsurgical tumor volumes and the clinical target volumes (V1, V2, and V3) calculated using the CT planning system were not significant prognostic indicators. Symptom duration and interval from surgery to radiotherapy also were not prognostic of survival time. Two patients whose tumors contained an oligodendrocytic component survived 36 and at least 60 months (the latter is still alive at the time of this report). The former underwent radiotherapy after reoperation for recurrence of a frontal GBM 10 months after the initial resection; he died without evidence of tumor, with findings from one biopsy sample having shown radiation necrosis only. A third patient, who is still alive at 37 months, had initially presented 8 years before detection of his GBM with a seizure following head trauma in a motor vehicle accident. Resection of a region revealed as hypodense on CT scanning had shown gliosis. This patient had been seizure free for 8 years when his GBM was detected. Thus, three of the patients with the longest survival times presented with known indicators of a more favorable prognosis: an oligodendrocytic component in two cases and, likely, a preexisting low-grade tumor in one.
Duration of Freedom From Imaging Changes

New gadolinium-enhancing areas were demonstrated on T₂-weighted MR images obtained in all patients during follow-up review. The median time to these changes from the time of first radiation treatment was 8 months. In all but one patient the changes were progressive, and they generally coincided with changes in T₁ signal intensity. The imaging changes correlated well with clinical deterioration (r = 0.89) in all but one patient who never deteriorated noticeably. In five cases, the changes on T₂-weighted images preceded the changes on T₁-weighted images by 3.5 weeks to 9 months; in one case, the T₁ change preceded the T₂ change by 3.1 months. There was a trend in which patients who developed imaging changes early had shorter survival time: eight (67%) of the 12 who showed changes within the first 8 months survived fewer than 20 months (Fig. 3 upper).

Location of Imaging Changes in Relation to Isodoses

In follow-up studies, new enhancement on MR imaging occurred first within the high-dose target volume (18 [78%] of 23 patients within the 90-CGE isodose). It extended beyond the designated target volume (V3, the largest volume, receiving 50.4 CGE) in only three cases (13%). In 11 of 23 patients, the lowest isodose associated with change was 60 CGE or less. No correlation was observed between isodose, imaging change, and time elapsed since radiation (Fig. 3 center and lower).

Pathological Findings at Reoperation or at Autopsy

Thirteen patients (57%) underwent at least one reoperation after completion of radiotherapy. In the group as a whole, 10 biopsy procedures and 12 resections were performed. Of the 13 patients who underwent a second procedure, biopsy samples were obtained in eight, and five underwent resection. Of the eight biopsy samples, six yielded necrotic material only. Of the five resections, four showed necrosis only, and one showed necrosis and recurrent tumor. Seven of the 13 patients underwent a third operation (one biopsy procedure, six resections). The biopsy sample showed necrosis and tumor; the resected material showed only necrosis in four cases and necrosis and recurrent tumor in two. Two patients underwent a fourth operation: one biopsy procedure and one resection, each of which retrieved necrotic tissue only. Taken together, eight patients underwent a significant resection at some point after radiation; three of them underwent multiple resections (Table 2). The survival time of those who underwent repeated resection did not differ significantly from those who did not. The repeated resection group might have fared considerably worse, however, if further surgery had not been performed.

We performed postmortem brain examinations in three patients after they had survived for 15, 17, and 19 months, respectively. One of them, who had an occipital lobe tumor, had undergone evacuation of a frontal hematoma 4 months before death and 11 months after the first surgery. Because no recurrent tumor was found and the site of surgery was remote from the original tumor site, this procedure is not counted among the reoperations for tumor resection described earlier. This patient had shown progressive imaging changes at both the occipital site and across the corpus callosum. The immediate cause of death was identified as massive thrombosis of the great cerebral vein. Recurrent tumor was found in the dose gradient between 64 CGE and lower doses, but only necrosis was found in higher-dose regions. In the second patient, biopsy sampling of an area of imaging change 8 months after the first surgery showed necrosis only. On autopsy we found recurrent tumor in areas subjected to lower doses but radiation necrosis only in the high-dose volume. The third patient died of recurrent tumor 19 months after diagnosis. At 9 months, his first imaging changes appeared both at the original site and separate from it. He received three courses of procarbazine, carboplatin, and vincristine chemotherapy before he died. His autopsy results showed recurrent tumor outside the high-dose volume and radiation necrosis within it. Thus, all three autopsies revealed recurrent tumor. In only one case has recurrent tumor been found within the 90-CGE volume (positive biopsy result; patient alive at 22 months).

Pathological material was available in 15 (65%) of 23 patients. Six of them never developed pathological evidence of tumor recurrence. One patient in whom no pathological material was obtained developed new gadolinium-enhancing areas on T₂-weighted MR images obtained 31 months after the first radiation treatment. She is alive and well at 60 months, and the original imaging changes have resolved. Her clinical course thus indicates necrosis only. The remaining 16 patients are thought to have had a mixture of radiation necrosis and recurrent tumor. Seven patients in whom no tissue was available to study are thought to have died of recurrent tumor on the basis of the pattern of imaging changes, clinical course, and inference from our autopsy experience. Nine patients had demonstrable recurrent tumor on pathological studies, as well as extensive radiation necrosis. The seven with only necrosis had a median survival time of 29 months compared with 16 months of those thought to have had both tumor and necrosis (p = 0.01; Fig. 4).

Discussion

The results reported here compare favorably with those of other series in which external-beam radiotherapy was...
months. Another comparison can be made with a recent trial reported by Pickles, et al., in which patients treated with conventional megavoltage x-ray therapy to 60 Gy in 30 fractions were compared with those treated using pion therapy. Selection criteria in their trial were similar to those reported here. The median survival time of 42 patients randomized to conventional therapy was 10 months, identical with the median survival time of those randomized to pion therapy. Because all patients underwent 3-D CT-based treatment planning, a comparison of the size of the clinical target volume was feasible. The gross clinical target volume in the photon group (defined by the 90% isodose and thus slightly larger than the drawn target) was 42 ml, only slightly more than the 36 ml defined as the high-dose target volume (V1) without added margin in our group. A major difference is the larger number of biopsy-only procedures in their series. Our patients generally underwent more aggressive surgery. However, this advantage may be balanced by the presence of approximately 25% of Grade III/IV tumors in their patient population.

The longer survival times in the group who had radiation necrosis only, compared with the group who had recurrent tumor and necrosis, also indicates that a positive effect of treatment, rather than selection bias, accounts for these superior results. Given the consistency of the trend, we estimate that the treatment-induced survival time benefit ranges from 5 to 11 months.

This cannot distract from the fact that the overall results are rather disappointing. The survival time curve has shifted to the right without an indication of a substantially higher plateau. This indicates a delay of death rather than a higher rate of cure, and even this is achieved only with additional surgery in some cases and progressive disability secondary to radiation necrosis and the side effects of steroid treatment in almost all. In most patients, the quality of life in the last 3 to 4 months was poor.

Without tissue sampling to differentiate radiation necrosis from recurrent tumor, the interpretation of our results would have been quite different, as 78% of the first imaging changes occurred within the confines of the highest isodose. Pathological specimens from biopsy sampling, repeated resection, and autopsies, however, demonstrated that these changes predominantly represented radiation necrosis. When doses are sufficiently high to risk a high incidence of radiation necrosis, radiographic change (enhancement) must not be assumed to reflect tumor recurrence and to constitute treatment failure. Additionally, considerable uncertainty exists in the histopathological interpretation of material that has been so heavily irradiated. Distinguishing between “residual” and “recurrent” tumor is notoriously difficult. Sampling errors can confound results of both biopsy procedures and limited resection. Three of our patients underwent autopsies; all had recurrent tumor, albeit outside the high-dose target volume, in combination with radiation necrosis. The absence of tumor within the 90-CGE target volume in all but one case suggests that this dose, delivered in accelerated fractionation, is sufficient for very high rates of tumor control. The prolongation of the median survival time shown here may represent the longer time needed for solid tumor to regrow in more peripheral areas containing a lower density of malignant cells; these cells become clinically determinant when control of tumor in more central areas is achieved.

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A variety of other methods of dose escalation have been explored during the last decade, most notably brachytherapy and radiosurgery. Phase II brachytherapy studies at first seemed to indicate an impressive increase in median survival time. However, more rigorous assessment of these studies has shown that this was largely the result of patient selection or early reporting: when the results of longer follow-up time were reported, median survival times declined from 27 to 18 months in the final report on the same series. Target volumes were small; the median rarely exceeded 22 ml. In addition, patients whose disease progressed during the conventional part of therapy were excluded from the analysis. When they were analyzed together with patients who actually received brachytherapy, the median survival time declined from 88 to 67 weeks. The Brain Tumor Cooperative Group study 8701, a randomized trial of up-front brachytherapy compared with no brachytherapy, is likely to allow more accurate assessment of survival benefit (SB Green, et al., unpublished data). Radiosurgical boosts of 10 to 20 Gy supplementing conventional fractionated radiotherapy of 60 Gy have led to median survival times of 9.5 to 22 months in recently reported series. Again, a dependence on target size and patient selection seemed to be responsible for this noticeable variation: patients with the smallest target size (median 4.8 ml) achieved the longest median survival time, whereas the median survival time declined to 9.5 months with larger targets (median 16.4 ml). One series included children. The toxicity of radiosurgery is demonstrated by a small study from McGill University, in which the boost was given up front to avoid the bias of excluding patients whose disease progressed during conventional therapy. Of the 14 patients studied, one developed a grand mal seizure and two became somnolent within 10 weeks of radiotherapy. Two more developed radionecrosis, which led to unilateral blindness in one. The median survival time was only 40 weeks.

Our series distinguishes itself from brachytherapy and radiosurgical boost efforts not only in dose and fractionation but also in the treatment of larger gross target volumes (median 36 ml). Proton irradiation facilitates the conformal treatment of highly irregular target volumes, a substantial advantage over brachytherapy. Thus, fewer eligibility restrictions were placed on our population. All of our patients completed therapy, albeit one received a reduced dose. Using particle therapy with heavier particles than protons, some researchers have attempted to exploit potential radiobiological advantages. This was based partly on the assumption that hypoxic cells in brain tumors contribute significantly to the clinical radioresistance of these lesions. Heavier particles show a lesser oxygen effect than high-energy x-irradiation or protons; therefore, no differential sparing of hypoxic cells could be expected. However, these efforts have been largely unsuccessful. Recently reported results of neon ion beam therapy resembled those of conventional therapy for similarly selected patients, with a median survival time of 13 months. In a study by Pickles, et al., pi-mesons (pions) have been evaluated in the treatment of GBM with results virtually identical to conventional high-energy x-ray treatment with a median survival time of 10 months. The neutron trials of

Conclusions

Escalation of the radiation dose to 90 CGE with a combination of protons and photons in accelerated fractionation has led to central tumor control in most cases, although tumors continue to recur peripherally. Virtually all patients develop radiation necrosis, necessitating reoperation in some and contributing to progressive neurological deterioration in most. Those in whom necrosis only develops seem to live significantly longer than those with recurrent tumor and necrosis, with a median survival time of 29 months compared with 16 months, respectively (p = 0.01). Perhaps this reflects the greater focality of necrosis in this trial compared with others as a result of improved dose localization and homogeneity with the use of protons. One might conclude that the expansion of the high-dose target volume would lead to improvement in tumor control on the periphery. However, the toxicity associated with this approach would be even greater, and any advantage in tumor control might be lost through an increase in treatment-related death. As long as radiation necrosis of the brain is associated with a fatal outcome similar to tumor progression, dose escalation is not an approach with a reasonable chance of improving survival time by a large margin. Therefore, dose deescalation from 90 CGE might be combined with an expansion of the target volume. This, in turn, carries the risk of losing tumor control, which is a dilemma that has marked GBM therapy for many years. Alternatively, methods aimed at the prevention of necrosis could be combined with high-dose therapy, except that no such method is known at this time. In the setting of controlled clinical trials, proton radiotherapy for GBM is likely to be further explored in the future, with a reasonable expectation of a modest survival benefit. In our view, this must be done in combination with an innovative approach aimed at reducing toxicity. The latter concern is so significant that the estimated improvement in median survival time of 5 to 11 months, after accounting for patient

J. Neurosurg. / Volume 91 / August, 1999

259
selection factors, appears to be too modest a gain to warrant imitation of our experience without modification of the trial design.

References

Manuscript received August 6, 1998. Accepted in final form March 17, 1999.
This work was funded in part by National Institutes of Health Grant No. PO1 CA 21239.
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