Randomized trial of three chemotherapy regimens and two radiotherapy regimens in postoperative treatment of malignant glioma

Brain Tumor Cooperative Group Trial 8001

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Within 3 weeks of definitive surgery, 571 adult patients with histologically confirmed, supratentorial malignant gliomas were randomly assigned to receive one of three chemotherapy regimens: BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea) alone, alternating courses (every 8 weeks) of BCNU and procarbazine, or BCNU plus hydroxyurea alternating with procarbazine plus VM-26 (epipodophyllotoxin). Patients accrued in 1980 and 1981 were to receive 6020 rads of whole-brain radiotherapy concurrent with the first course of chemotherapy. Patients accrued in 1982 and 1983 were randomly assigned to receive either whole-brain irradiation as above, or 4300 rads of whole-brain radiotherapy plus 1720 rads coned down to the tumor volume. The data were analyzed for the total randomized population and separately for the 510 patients, termed the "Valid Study Group (VSG)," who met protocol eligibility specifications (including central pathology review), 80% of whom had glioblastoma multiforme. The median survival times from time of randomization for the three chemotherapy groups of the VSG ranged from 11.3 to 13.8 months, and 29% to 37% of the patients survived for 18 months (life-table estimate); the differences between these groups were not statistically significant. Survival differences between the radiotherapy groups were small and not statistically significant. It is concluded that, for malignant glioma, giving part of the radiotherapy by coned-down boost is as effective as full whole-brain irradiation, and that multiple-drug chemotherapy as outlined in this protocol conferred no significant survival advantage over BCNU alone.

KEY WORDS - brain neoplasm - chemotherapy - radiation therapy - multicenter study - BCNU

The Brain Tumor Cooperative Group (BTCG), previously named the Brain Tumor Study Group, has conducted a series of randomized clinical trials investigating various multimodality treatment regimens for malignant gliomas. The latter include the glioblastoma multiforme, the anaplastic astrocytoma, and an assortment of other malignant gliomas. These studies included Phase III protocols consisting of randomized prospective trials of surgery, various modalities of radiation therapy, and chemotherapy in newly diagnosed patients, and Phase II chemotherapy protocols in patients previously treated with radiation therapy. The BTCG Phase III studies produced the following results: 1) radiotherapy (6000-rad whole-brain dose) following surgery resulted in longer survival than surgery without additional specific therapy (Trial 6901); 2) chemotherapy with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) offered an additional modest improvement in survival, with a larger percentage of patients surviving more than 18 months than in the group treated with surgery and radiation therapy without BCNU (Trials 7201 and 7501); 3) high-dose methylprednisolone did not lead to longer survival (Trial 7501); 4) procarbazine and streptozotocin each showed similar effectiveness to BCNU (Trials 7501 and 7702); and 5) neither the increased fractionation (twice daily) of radiotherapy nor addition of the radiosensitizer misonidazole conferred any survival ad-
vant over the conventional postoperative use of whole-brain radiotherapy and BCNU (Trial 7702). One Phase II trial demonstrated that 1-(2-chloroethyl)-3-(2,6-dioxo-3-piperidyl)-1-nitrosourea (PCNU) was an effective agent when compared to aziridinylbenzoziquinone (AZQ). Other trials tested (and generally found to be ineffective) a number of other chemotherapeutic agents.

All of the Phase III trials and all but two of the Phase II trials tested single-agent chemotherapy. However, many successful chemotherapy programs for systemic cancers have used polychemotherapy (several drugs administered simultaneously or sequentially). Furthermore, studies by Shapiro, et al., demonstrated that human malignant gliomas are heterogeneous (that is, composed of many genotypically and phenotypically different cell populations). Among the phenotypic differences is marked variability in chemosensitivity to BCNU and cisplatin of individual clones from single tumors. These studies suggested that multiple-drug chemotherapy might be more successful than single drugs, because individual tumor cells would have several agents available to kill them. Clearly, polychemotherapy would be most effective if the sensitivities of the tumor cells were known and specifically effective drugs were administered. In the absence of such data, drugs could be chosen empirically, based on previous experience with single-agent studies, a technique that had been successful with systemic cancer. The result was Trial 8001.

The first aim of Trial 8001 was to compare in a randomized study three chemotherapeutic regimens: 1) BCNU alone; 2) alternating courses (every 8 weeks) of BCNU and procarbazine; and 3) BCNU plus hydroxyurea (HU), alternating with procarbazine plus VM-26 (epipodophyllotoxin). The drugs used in the multidrug arms were chosen from previous BTCG Phase III and II studies.

Procarbazine is a water-soluble N-methylhydrazine. Its mechanism of action is unknown, but it appears to produce chromosomal breakage as well as inhibit protein synthesis, and it therefore resembles an alkylating agent. Despite its water-solubility, it readily crosses the blood-brain barrier (BBB) and may produce mild central nervous system toxicity. Its major toxicity is myelosuppression, but it often causes nausea and vomiting and may rarely cause a severe rash. Pharmacological studies have indicated excellent gastrointestinal absorption with rapid equilibration between plasma and cerebrospinal fluid in dogs and man. Procarbazine is a standard chemotherapeutic agent used in the treatment of Hodgkin's disease, malignant melanoma, and a variety of other cancers. Results of a controlled Phase III study (BTCG 7501) indicated that procarbazine is as active a drug as BCNU and provides comparable survival. It is therefore a drug that can replace BCNU in other combinations and could have an additive effect when used in combination with BCNU. Thus, procarbazine appeared an ideal choice as a second drug to be given with BCNU. Because procarbazine is a profound marrow suppressant and must be administered in reduced dosage when combined with other marrow-suppressant drugs, it was given sequentially with BCNU when both drugs could be given at full dosage.

Hydroxyurea is a cell cycle-specific drug that interferes with deoxyribonucleic acid (DNA) synthesis through inhibition of ribonucleoside diphosphate reductase. This enzyme catalyzes the reductive conversion of ribonucleotides to deoxyribonucleotides, which are necessary for DNA synthesis. Hydroxyurea readily crosses the BBB, despite its water-solubility. Toxicity is primarily anorexia, nausea, vomiting, and occasional stomatitis, as well as dose-limiting reversible leukopenia, thrombocytopenia, and anemia.

Epipodophyllotoxin is a semisynthetic podophyllotoxin of large size which is highly lipophilic. The drug is a mitotic spindle poison like the vinca alkaloids. It has been found to be taken up by cells by passive diffusion and binds to high- and low-affinity binding sites. This drug binds to tubulin, a microtubule subunit, and in vitro causes a premitotic delay with cells irreversibly accumulating in the G2 phase of the cell cycle. It is a cell cycle-specific drug. Despite its high lipophilicity, only minimal amounts cross the BBB, although the drug has been reported effective against some malignant gliomas in Phase II trials. The major dose-limiting toxicity of VM-26 is hematological, although this is not cumulative.

Interim analyses of BTCG Phase II studies indicated that HU and VM-26 might be of potential value in the treatment of malignant gliomas and therefore should be considered for Phase III study. Their relative marrow-sparing characteristics made them good choices for combination chemotherapy with BCNU and procarbazine.

The second consideration in Trial 8001 related to the radiation therapy protocol. All previous BTCG protocols had used whole-brain irradiation exclusively rather than irradiation to the tumor alone. This choice was based on earlier clinicopathological correlation studies before the advent of computerized tomography (CT), which confirmed the likelihood of under-radiating tumors using dosimetry based on then-available radiological localizing techniques. However, many studies, including those of the BTCG, indicated that high-dose whole-brain irradiation produced brain damage, characterized by slowly progressing dementia associated with white matter hypodensity on CT scans. These findings had already led some investigators to reduce part or all of the radiotherapy portals to the region of tumor as defined by the CT scan. The problem was that no one had shown that reducing radiation portals might not also reduce radiation effectiveness. For this reason, it was elected to modify Trial 8001 midway in its course to compare entirely whole-brain irradiation with a regimen involving some whole-brain and some coned-down focal irradiation. Patients accrued in 1980 and 1981 were to receive 6020-rad whole-brain radiother-
apy concurrent with the first course of chemotherapy. Patients accrued in 1982 and 1983 were randomly assigned to receive either whole-brain irradiation as above, or 4300-rad whole-brain irradiation plus 1720 rads coned down to the tumor volume. Besides addressing the issue of the effectiveness of coned-down compared to whole-brain radiation therapy, the protocol would eventually permit comparison of the toxicity of the two programs. In all cases the basic design remained prospective, randomized, and controlled. The questions asked in the two therapy trials could be answered independently. Thus, the study addressed both a chemotherapy and a radiotherapy question using the principles of factorial design.

Clinical Material and Methods

Patient Accrual

Seven institutions participated in the design and conduct of this trial (see Appendix). Patients were to be entered in the study by the principal investigators at each institution within 3 weeks of definitive surgical treatment for the primary tumor. Eligibility criteria included the presence of a histologically demonstrated supratentorial malignant glioma, a patient age of 15 years or greater, the absence of other major illness which might preclude treatment on any arm of the study, and a Karnofsky performance status of 40 or greater at the time of randomization. Eligible patients were not to have received any previous antineoplastic therapy, but conventional doses of corticosteroids were allowed. Written informed consent was obtained from all patients. Before randomization, the best possible conventional neurosurgical procedure was performed. In particular, maximum tumor resection and internal cerebral decompression commensurate with good medical judgment was accomplished in all patients. A set of pathology slides from each patient’s tumor was sent to the BTCG Operations Office for subsequent evaluation by the Neuropathology Review Committee, which made the final determination of eligibility on the basis of defined histopathological criteria.

Chemotherapy Treatment

Patients were randomly assigned by means of a telephone call to the BTCG Operations Office, to one of the three treatment regimens.

Arm 1: Radiotherapy and BCNU. In Arm 1, radiation therapy was administered as follows. Patients received BCNU, 80 mg/sq m/day, administered intravenously over 30 to 60 minutes for 3 days. According to protocol, this dose of BCNU was repeated at 8-week intervals if the platelet count nadir was not below 50,000/cu mm, the white blood cell (WBC) count nadir was not below 2500/cu mm, or the hematocrit drop was not greater than five points, and if the recovery platelet count was over 100,000/cu mm, the WBC count was greater than 3500/cu mm, and the hematocrit was greater than 35%. A reduced BCNU dose of 60 mg/sq m/day for 3 days was administered if the nadir counts reached the limits described above, and recovery exceeded a platelet count of 75,000/cu mm, a WBC count of 3000/cu mm, and a hematocrit of 30%. A further reduction in BCNU to 45 mg/sq m/day was ordered if the same indicators of hematotoxicity were observed after treatment at a reduced dose. If the nadir counts mentioned above were reached after BCNU doses of 45 mg/sq m/day, no further BCNU was administered.

An additional restriction for total cumulative BCNU administration was related to the potential for pulmonary toxicity. Aronin, et al.,2 showed that BCNU can produce pulmonary fibrosis. For this reason, pulmonary function studies were performed in all patients. Initial studies were performed before the start of BCNU therapy to provide a baseline (reference) value to which the results of subsequent tests could be compared. The pulmonary function tests were repeated prior to the courses of treatment when the total cumulative amount of BCNU given would exceed 800 mg/sq m (the fourth course if full doses of BCNU had been utilized) and 1200 mg/sq m (the sixth course if full doses of BCNU had been utilized). No further BCNU was given after the course of treatment that brought the total cumulative amount of BCNU in excess of 1500 mg/sq m. The carbon monoxide single-breath diffusion test was considered to be the most sensitive single assessment and was always performed. Patients exhibiting a dry, hacking cough or other pulmonary-related problem at any time during their course of treatment with BCNU underwent a chest x-ray study and a pulmonary function test(s). If at any time the results of subsequent carbon monoxide diffusion tests indicated a decrease of 15% or more from the baseline value (% of predicted), then treatment with BCNU was discontinued.

Arm 2: Radiotherapy and Alternating Courses of BCNU and Procarbazine. In Arm 2, radiation therapy was administered as follows. The two drugs were administered alternatively every 8 weeks. The BCNU was given as described in Arm 1 and the procarbazine was administered orally at 150 mg/sq m in three or four equally divided doses per day for 28 days. Retreatment with procarbazine after the BCNU cycle was to be at 16-week intervals with dosage modifications based on the hematotoxicity criteria outlined for BCNU in Arm 1. In the event of severe toxicity as a result of a prior dose of procarbazine or BCNU, procarbazine was utilized at a reduced dose of 100 mg/sq m/day for 28 days. During the subsequent cycles of procarbazine a further reduction to 80 mg/sq m/day for 28 days was undertaken if retreatment on the reduced dose indicated excessive toxicity. Serious leukopenia (WBC count < 2500/cu mm) and thrombocytopenia (platelet count < 50,000/cu mm) after two dose reductions was an indication for discontinuation of the drug.

A rare but specific complication of procarbazine was a severe rash, which could develop at any time in the treatment course. The development of such a rash was
an indication to discontinue the drug. If during the course of treatment one of the two drugs had to be discontinued because of a complication (such as change in pulmonary status or development of a rash), the other drug was continued every 16 weeks.

Arm 3: Radiotherapy and Alternating Courses of BCNU Plus Hydroxyurea and Procarbazine Plus VM-26. In Arm 3, radiation therapy was administered as follows. Hydroxyurea and BCNU were given as combination chemotherapy for an 8-week course; for the next 8-week course, procarbazine and VM-26 were administered in combination. Then BCNU and HU were administered in subsequent 8-week courses alternating with procarbazine and VM-26.

The BCNU was administered as in Arm 1. Hydroxyurea treatment started the day after completion of BCNU treatment and was administered orally at a dose of 1000 mg/sq m/day every other day in four equally divided doses (250 mg/sq m) for a total of 21 days of therapy. Severe thrombocytopenia or leukopenia was an indication for temporary discontinuation of HU until evidence of return to acceptable function. Repeat treatment was started at one-half the prescribed dose (500 mg/sq m divided into four daily doses every other day). Severe toxicity at one-half the dose was an indication for further dose reduction to approximately one-third the prescribed dose (350 mg/sq m/day in four equally divided doses every other day). The treatment was discontinued in cases of severe nausea, vomiting, diarrhea, or stomatitis.

Procarbazine was utilized as described in Arm 2 for 28 days. Treatment with VM-26 was begun simultaneously with the procarbazine and was administered at 130 mg/sq m once per week for 6 weeks. A treatment course consisted of 6 weeks of therapy and 2 weeks without therapy. To obviate hypotension with rapid drug administration, VM-26 was diluted with 250 ml of normal saline and delivered over a 1-hour period. Additional courses used the same therapeutic schedule unless there was evidence of toxicity.

Radiation Treatment

Radiotherapy was begun within 3 weeks after surgical resection in conjunction with chemotherapy as prescribed above. Treatment was delivered only by megavoltage equipment with a source-axis distance of not less than 80 cm and a midplane dose rate of not less than 33 rads/min. The radiation therapy was given in one continuous course.

For the whole-brain only procedure, the total dose was 6020 rads (approximately 1700 rets), delivered to the tumor with the 90% isodose contour encompassing the target volume (tumor plus 2 cm margin). The whole-brain irradiation portion of this procedure utilized 4300 rads in 25 fractions of 172 rads each over 5 weeks via bilateral opposing ports. A coned-down boost of 1720 rads was given in 10 fractions over 2 weeks following the whole-brain radiation therapy. The coned-down volume was determined by defining the volume of the tumor prior to initiation of radiation therapy and allowing for a margin of at least 2 cm, but sparing as much brain as possible.

Ancillary Treatment

Anticonvulsant medications were used as necessary to control seizures. Corticosteroids were used in all treatment groups as needed for the control of cerebral edema.

Statistical Considerations

This study was a three-arm randomized clinical trial of chemotherapy. It was also a trial comparing whole-brain radiation therapy with partially whole-brain radiotherapy plus a coned-down portal. Comparisons in survival were made among the radiation therapy and chemotherapy groups. The probability of survival was calculated for a specific length of time by the life-table method and compared with survival of different groups using a Mantel (log-rank) statistic, always with two-tailed tests. In addition, median survival periods of the treatment groups adjusted for important prognostic factors were compared using a Cox proportional-hazards model. Testing for significance of treatment effects was based on likelihood ratio statistics. Score statistics were used to identify possible important interaction terms, which were tested formally with likelihood ratio statistics.

The radiotherapy randomization permitted the study to be analyzed by factorial design. All patients entered in the study contributed to the analysis of the primary chemotherapy question. Those patients randomly assigned during the second part of the study to one of the two radiotherapy alternatives contributed to the radiotherapy comparison.
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### TABLE 2
Characteristics of patients in the Valid Study Group

<table>
<thead>
<tr>
<th>Patient &amp; Tumor Characteristics</th>
<th>Treatment Group*</th>
<th>All Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RT + BCNU</td>
<td>RT + BCNU/ PCZ</td>
</tr>
<tr>
<td>no. of cases</td>
<td>166</td>
<td>176</td>
</tr>
<tr>
<td>age at randomization (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–44 yrs</td>
<td>21.7</td>
<td>22.2</td>
</tr>
<tr>
<td>45–54 yrs</td>
<td>24.1</td>
<td>22.2</td>
</tr>
<tr>
<td>55–64 yrs</td>
<td>33.7</td>
<td>33.0</td>
</tr>
<tr>
<td>65+ yrs</td>
<td>20.5</td>
<td>22.2</td>
</tr>
<tr>
<td>Karnofsky performance status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90–100</td>
<td>28.3</td>
<td>22.2</td>
</tr>
<tr>
<td>70–80</td>
<td>29.5</td>
<td>31.3</td>
</tr>
<tr>
<td>50–60</td>
<td>33.1</td>
<td>8.5</td>
</tr>
<tr>
<td>histopathology (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>glioblastoma multiforme</td>
<td>81.3</td>
<td>79.0</td>
</tr>
<tr>
<td>anaplastic astrocytoma</td>
<td>18.7</td>
<td>21.0</td>
</tr>
</tbody>
</table>

* RT = radiation therapy; PCZ = procarbazine; HU = hydroxyurea.

Results

The data were analyzed for the total randomized population group (RPG) and separately for those patients who met protocol eligibility specifications (including central pathology review), termed the “Valid Study Group (VSG).” The total number of patients randomly assigned to groups was 571 (shown by treatment assignment in Table 1). The age range was 15 to 84 years (median 56 years).

There were 510 patients in the VSG. The reasons for exclusion were as follows: 45 patients did not have malignant glioma on neuropathological review of slides; in three cases not enough material was available for neuropathological review; 12 patients were accrued in error (11 had, at most, a needle biopsy and one suffered major intercurrent illness); and one patient was lost to follow-up review immediately after randomization. Two patients who had Karnofsky performance status scores of 30 were retained in the VSG, although technically they did not meet the cutoff value of 40. The characteristics of the VSG are listed in Table 2 by treatment group. It is of note that 80% of the patients had glioblastoma multiforme. The definition “anaplastic astrocytoma” covered 104 patients; however, the actual pathological diagnoses of these patients’ tumors were: anaplastic astrocytoma (79 cases), anaplastic oligodendroglioma (four cases), anaplastic ependymoma (four cases), and malignant glioma (not otherwise specified, 17 cases).

Survival data were analyzed for both the RPG and the VSG. At the time of analysis, 469 of the 571 patients in the RPG had died; the median follow-up time from randomization for the 102 patients last known alive was 52 months (range 0 to 84 months). Figure 1 shows the length of survival (from time of randomization) by chemotherapy group for the RPG and for the VSG. Differences were analyzed by the Mantel statistic (equivalent to the log-rank test). Overall heterogeneity across the three curves was not statistically significant (p = 0.33 for the RPG, 0.59 for the VSG) and thus is consistent with chance. As seen in Fig. 1 right and Table 3, median survival times for the VSG ranged from 11.3 to 13.8 months, and 29% to 37% of the patients survived 18 months (life-table estimate).

Figure 2 shows survival by assigned radiotherapy group for the RPG and the VSG. Overall heterogeneity was not statistically significant (p = 0.30 for the RPG, 0.62 for the VSG), nor were any of the pairwise comparisons significant. Here, of course, it is specifically the comparison of the two randomized radiotherapy arms in 1982 and 1983 which is of interest; for this comparison, p = 0.21 for the RPG and 0.34 for the VSG.

Analyses of other variables in these data showed that histopathological category (Fig. 3), age at randomization (Fig. 4), and Karnofsky performance status at randomization (Fig. 5) were all markedly significant prognostic variables (p < 0.00001 for each variable considered separately), consistent with results in former studies.

![Fig. 1](https://example.com/image1.png)  
**Fig. 1.** Graphs showing survival time from time of randomization correlated with chemotherapy group for the total randomized population (571 patients, left) and the Valid Study Group (510 patients, right). PCZ = procarbazine; HU = hydroxyurea. Numbers in parentheses denote numbers of patients in each group.

![Fig. 2](https://example.com/image2.png)
TABLE 3

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. of Cases</th>
<th>Median Survival Time (mos)</th>
<th>Mean Percent Surviving ± Standard Error of the Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>radiation therapy + BCNU</td>
<td>166</td>
<td>13.1</td>
<td>54.2 ± 3.9 28.8 ± 3.5 21.3 ± 3.2 16.4 ± 3.0</td>
</tr>
<tr>
<td>radiation therapy + BCNU/procarbazine</td>
<td>176</td>
<td>11.3</td>
<td>45.1 ± 3.8 31.6 ± 3.6 22.0 ± 3.2 11.5 ± 2.6</td>
</tr>
<tr>
<td>radiation therapy + BCNU + hydroxyurea/</td>
<td>168</td>
<td>13.8</td>
<td>56.0 ± 3.8 37.4 ± 3.7 25.7 ± 3.4 11.8 ± 2.8</td>
</tr>
<tr>
<td>procarbazine + VM-26</td>
<td></td>
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</tbody>
</table>

A Cox proportional-hazards model was applied to study the survival profile in the VSG, incorporating these three prognostic variables as well as indicator variables for the various chemotherapy and radiotherapy groups. Results indicated that, although age was quite important prognostically in both histopathological subgroups, the effect of age was more pronounced for the anaplastic astrocytomas, so an interaction term was included to model this effect. The three prognostic variables were all significantly predictive when included together in the model, but the treatment variables were not statistically significant. Thus, using the model to adjust for multiple variables did not change the conclusions.

Subsidiary analyses were performed separately for the two histopathological subgroups of the VSG. No differences between radiotherapy groups were seen in either subgroup. Survival curves (not shown) for the three chemotherapy groups among only glioblastoma patients revealed a modest trend for better survival with increasing numbers of agents. However, among anaplastic astrocytoma patients, the group receiving only BCNU had the best survival times. In Cox models, these treatment differences were notably smaller (and no longer statistically significant) when adjusted for age and Karnofsky performance status, reflecting the chance imbalances that can occur in subsets. A formal likelihood ratio test for interaction of treatment with histopathology (testing whether the treatment effects differed between the two subgroups) was highly significant in the absence of adjustment, but was only of borderline significance (p = 0.06) when adjusted for the other prognostic factors. These findings in the subset analyses most likely represent chance fluctuations.

In two previous studies, the BTCG had noted an apparent prognostic effect associated with blood type, with the presence of blood group A (whether A or AB) predicting decreased survival times compared to types B and O. A similar analysis was performed in this study. Survival curves (not shown) for these two subcategories in the current study showed that patients with type A or AB blood had a slightly better survival time than those with type B or O (p = 0.02), an effect in the opposite direction to that seen previously. In a Cox model adjusted for histopathology, age, and performance status, this effect was smaller and not statistically significant. Thus, this study fails to support the previously suggested effect.

Adverse events representing possible toxicity were summarized over all courses of chemotherapy received by the study patients and are presented separately by randomized treatment assignment (Table 4). In addition to specific data on clinical hematology and chemistry, qualitative information was collected as to the incidence of a variety of adverse medical sequelae, according to a checklist submitted to the BTCG Oper-
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Fig. 3. Graph showing survival time from time of randomization correlated with the histopathological diagnosis. Numbers in parentheses denote numbers of patients in each group.

Fig. 4. Graph showing survival time from time of randomization correlated with patients' age at randomization. Numbers in parentheses denote numbers of patients in each age group.

Fig. 5. Graph showing survival time from time of randomization correlated with Karnofsky performance status at randomization. Numbers in parentheses denote numbers of patients in each group.

TABLE 4
Percent of patients in each randomized arm for whom adverse events were reported*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RT + BCNU</td>
</tr>
<tr>
<td>WBC &lt; 2000/cu mm</td>
<td>16.8</td>
</tr>
<tr>
<td>platelets &lt; 50,000/cu mm</td>
<td>18.4</td>
</tr>
<tr>
<td>hematocrit &lt; 25%</td>
<td>5.4</td>
</tr>
<tr>
<td>abnormal liver function†</td>
<td>4.8</td>
</tr>
<tr>
<td>abnormal renal function†</td>
<td>2.7</td>
</tr>
<tr>
<td>pulmonary fibrosis</td>
<td>5.4</td>
</tr>
<tr>
<td>allergic reaction (rash)</td>
<td>7.6</td>
</tr>
<tr>
<td>infection</td>
<td>27.0</td>
</tr>
<tr>
<td>severe nausea/vomiting/diarrhea</td>
<td>1.6</td>
</tr>
</tbody>
</table>

* RT = radiation therapy; PCZ = procarbazine; HU = hydroxyurea; WBC = white blood cells.
† For chemical testing, any occurrences of toxicity levels 3 to 5 (on a 0 to 5 scale) are tabulated.

the promise offered by the rationale was not borne out in the results. Giving multiple-drug chemotherapy as outlined in this protocol conferred no significant survival advantage over BCNU alone.

Polychemotherapy has been used for malignant glioma in Phase II chemotherapy studies throughout the world. Many of these studies were reported as showing substantial advantage for the multidrug regimen over (usually historic) control series utilizing BCNU alone. Response rates of 40% to 60% were reported in these studies. As has been observed in the past, such optimistic results could not be translated into prolonged survival in Phase III studies utilizing a concurrent control group. In part, this failure reflects the difference in the kinds of patients entered into Phase II and Phase III studies. In the former, patients usually have recurrent disease, yet often must be well enough to have a Karnofsky performance status score of at least
radiation field, followed by a coned-down field, as Un-
coned-down radiation. Recently, some radiation oncol-
is clear that the CT scan does permit localization for
majority of single gliomas can be treated with a large
indicated only when there are multiple lesions; the
oncologists have suggested that whole-brain radiotherapy is
limited studies, ~3 and still holds promise for the future.
merits will add to the survival time achieved by this
surgery of whether the tumor excision was a gross total or
significant relationship with post-
our early studies.
The next issue relates to polychemotherapy as a
heterogeneity of gliomas.
Chemosensitivity testing has been tried in
still holds promise for the future.
use the technique to design rational polychemotherapy;
indeed, few in vitro studies have even tried multiple-
Further, the presence of tumor hetero-
confounds this attempt at a solution. Unless
enough of a tumor is sampled and tested, the results
likely to be sufficiently representative of the
majority of the tumor to suggest a predictable prescrip-
How this problem will be solved awaits future
The next question posed by this trial relates to the
issue of the radiation portals. Here, the answer was
positive. Giving part of the radiotherapy by coned-
boost is as effective as full whole-brain irradiation.
We thus have no hesitation in recommending this
technique does not compromise efficacy.
An additional issue posed by this study is related to
the extent of radiation damage likely to be produced by
whole-brain radiotherapy at 6000 rads. The trial design of
both longitudinal and horizontal comparisons should
make it possible to detect differences in cognition, motor,
and sensory symptoms and alterations on CT
scans indicative of radiation damage to the brain. Such
an analysis must be based on relatively long-term sur-
vivors and is planned in the near future.
As in previous studies, this trial again confirmed the
prognostic importance for survival of patients with
malignant glioma of the patients' age, Karnofsky per-
formance status, and tumor histopathology. In a sepa-
rate publication, we examined the prognostic impor-
tance of tumor size (measured on CT scans) at different
time points, and we found no relationship between
preoperative tumor size and ultimate survival time;
however, there was a significant relationship with post-
operative size. Tumors with a cross-sectional area of 1
sq cm or less after surgery were associated with substan-
tially longer survival than were larger tumors. In addi-
tion, the amount of tumor remaining after irradiation
was significantly related to survival time. Information
on the size of tumor as visualized on CT scans was not
available for all of the patients; however, we did have
available for each patient the assessment at initial sur-
ertainment whole-brain and coned-down radiotherapy plus
chemotherapy with a nitrosourea. Only future studies
will dictate which of several experimental new treat-
ments will add to the survival time achieved by this
regimen.

APPENDIX

The institutions, National Institutes of Health grant num-
ers, principal investigators, and contributing investigators in
this project were: Memorial Sloan-Kettering Cancer Center
(CA 36047), William R. Shapiro, M.D., Jae Ho Kim, M.D.,
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