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● *Clinical Investigation*

SHORT COURSE RADIOTHERAPY IS AN APPROPRIATE OPTION FOR MOST MALIGNANT GLIOMA PATIENTS

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Purpose: To determine whether a shortened course of radiotherapy (RT) is an appropriate treatment option for malignant glioma patients.

Methods and Materials: Prognostic groups published by the Radiation Therapy Oncology Group (RTOG) are used to compare results for a short radiotherapy regimen with results of aggressive protocol treatment. The study group includes 219 patients treated during 1975–1993 with 51 Gy in 17 fractions. Patients were retrospectively assigned to six prognostic groups previously identified in a recursive partitioning analysis of the RTOG. The prognostic groups are based on age, histology, performance status, mental status, neurologic function, resection extent, length of symptoms, and RT dose.

Results: The six RTOG prognostic groupings were significantly predictive of outcome for patients treated with this shortened regimen (log-rank, $p < 0.001$). The median survival for our patients by RTOG groups 1–6 were 68, 57, 22, 13, 8, and 5 months, respectively. Two-year survival results were 64, 67, 45, 8, 3, and 3%. The median and two-year survival results for each prognostic grouping were similar to the results achieved by aggressive treatment on RTOG malignant glioma trials for selected patients. Treatment toxicity was uncommon.

Conclusion: This shortened regimen is an appropriate treatment option for most malignant glioma patients (RTOG groups 4–6), resulting in similar survival as standard regimens with reduced patient effort and cost. Although acute side effects are acceptable and the risk of brain necrosis is low, we do not recommend this treatment to the minority of patients who have a substantial long term survival probability (RTOG groups 1–3) because long term neurocognitive assessment is lacking. © 1997 Elsevier Science Inc.

Radiotherapy, Malignan glioma, Glioblastoma, Anaplastic astrocytoma, Cost, Quality of life.

INTRODUCTION

The purpose of this study is to determine whether a shortened course of radiotherapy is an appropriate treatment option for malignant glioma patients by using prognostic groupings to compare survival results with previously published outcome data for patients treated aggressively on Radiation Therapy Oncology Group (RTOG) protocols.

Despite intense investigation of aggressive treatments, the prognosis for malignant glioma patients remains poor (2, 5, 6, 11, 12, 14, 15, 16). There are no therapeutic options applicable to most patients that have been shown to be substantially better than standard radiotherapy. Standard external beam radiotherapy for malignant glioma patients is 30–33 daily fractions to a total dose of approximately 60 Gy at 1.8–2.0 Gy a day. The addition of chemotherapy increases the length of survival of some patients, but does not significantly improve median survival.

Since survival for malignant glioma is poor, we and other investigators have used shorter treatment courses for poor prognosis patients rather than the standard 6–7 week course of daily radiotherapy (1, 7, 9, 13). Curran *et al.* (4) recently called for a "study of short courses of accelerated radiation" after identifying large subgroups of patients with a median survival of only 4–9 months and two-year survival of only 4–6% despite aggressive treatment on RTOG protocols. A standard review text commonly used by neurology students and house staff states that the "greatest morbidity that most patients suffer as a result of cranial irradiation is the extra 5–6 weeks during which they must . . . return each day" (17).

Curran *et al.* (5) have published prognostic groupings identified by a recursive partitioning analysis of the outcome of 1578 malignant glioma patients treated on RTOG protocols. The prognostic groups were based on tumor histology, age, performance status, extent of resection, mental status, and neurologic function prior to the start of radiation. Six groups were identified with median surviv-

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als varying from 4.6 to 58.6 months. The survival results for these groups of selected and aggressively treated RTOG patients can provide benchmarks for evaluating the results of alternative treatment regimens.

We have treated 224 patients with a short course 17 treatment regimen (SHORT) in the modern era since the development of routine CT scanning. In this study, the patients treated with our short course regimen are classified into the RTOG prognostic groups, and the outcome results are compared to patients treated aggressively on RTOG protocols. The toxicity of the short regimen and the role of adjuvant chemotherapy are examined.

MATERIALS AND METHODS

Patient population

Two hundred and twenty-four patients with malignant glioma who were treated with short course radiotherapy in the Division of Radiation Oncology at Johns Hopkins between 1975 and the end of 1993 were identified from the Johns Hopkins Tumor Registry. Five patients were excluded because the relevant prognostic factors could not be obtained from the available medical records. During those years, this was the standard treatment regimen for malignant glioma patients at our institution. Some patients were treated on protocol with neoadjuvant cisplatin and carmustine (BCNU) followed by SHORT radiotherapy or with concurrent Cisplatin/BCNU/radiotherapy.

Radiotherapy

The radiation treatment was 3.0 Gy × 10 given to a large or whole brain field. After a two week break, an additional 3.0 Gy × 7 was given to a reduced conedown field for a total dose of 51 Gy given in 17 visits over 5.5 weeks (SHORT regimen). When possible, the optic chiasm and brainstem were excluded from the conedown field. Poor prognosis patients were, in some cases, given the option of discontinuing treatment during the break if their condition was not improving. Of 170 patients for whom information about the size of the radiation field was available, 51% were treated to the whole brain for the initial 30 Gy.

Chemotherapy

Twenty-nine percent of the patients received chemotherapy as part of the initial treatment, and 10% as part of salvage therapy. Chemotherapy treatment was given both on protocols and ad hoc. All received nitrosourea-based regimens for at least a portion of their chemotherapy treatment.

Prognostic groups

The prognostic groups were identified by Curran *et al.* (4) using a recursive partitioning analysis of the combined results of three large RTOG malignant glioma randomized trials. The grouping criteria are summarized in Table 1. Eligibility for those studies was limited to patients age 18–70 with a Karnofsky Performance Status (KPS) of at least 40, with acceptable laboratory studies. In the present study, patients receiving the SHORT regimen were assigned to these prognostic groups based upon information available in postoperative surgical notes and consult records without knowledge of survival outcome.

Table 1. Prognostic groupings from analysis of RTOG database

I	< 50 yo, AAF, Normal mental status
II	> = 50 yo, KPS 70-100, AAF, Symptoms > 3 months
III	< 50 yo, AAF, Abnormal mental status
	< 50 yo. GBM, KPS 90-100
IV	< 50 yo, GBM, KPS < 90
	> = 50 yo, KPS 70-100, AAF, Symptoms < = 3 months
	> = 50, KPS 70-100, GBM, Resection, able to work
V	> = 50 yo, KPS 70-100, GBM, Resected, can't work
	> = 50 yo, KPS 70-100, GBM, biopsy, RT > 54.4 Gy*
	> = 50, KPS < 70, Normal mental status
VI	> = 50 yo, KPS 70-100, GBM, Biopsy, RT < = 54.4 Gy*
	> = 50 yo, KPS < 70, Abnormal mental status

AAF = astrocytoma with anaplastic or atypical focus. In the present study this included tumors called "anaplastic" or "Grade III" astrocytoma.
yo = years old.
KPS = Karnofsky Performance Status.
GBM = Glioblastoma Multiforme.
* In the SHORT regimen, full dose RT was considered to be > 45 Gy.

Toxicity

Information about acute toxicity including clinical deterioration or increased steroid requirements was abstracted from treatment records. All pathology reports from reoperations and autopsy results were reviewed for indication of radiation necrosis.

Follow-up

Follow-up information was available from charts and tumor registry information. Six patients were lost to follow-up while still alive, and 15 were alive at the time the data were finalized.

Statistical methods

The cumulative probability of surviving a given length of time was computed using the Kaplan-Meier product limit method for each of the prognostic groups (3). Survival curves were compared using the log-rank test (8). Survival was measured from date of surgical procedure.

RESULTS

Patient characteristics

The characteristics of the patients are summarized in Table 2. The distribution among the prognostic groups was: Group 1: 14; Group 2: 3; Group 3: 29; Group 4: 64; Group 5: 68; Group 6: 40.

Table 2. Characteristics of patients

Age (years)	
< 50	73 (33%)
> = 50	146 (67%)
Histology	
Glioblastoma	185 (84%)
Anaplastic astrocytoma	34 (16%)
Karnofsky performance status	
> = 70	156 (72%)
50-60	57 (26%)
<50	5 (2%)
Unknown	1 (0.5%)
Mental status	
Abnormal	61 (27%)
Normal	158 (73%)
Extent of surgery	
Biopsy only	55 (25%)
Resection	164 (75%)
Chemotherapy in initial treatment	
No	155 (71%)
Yes	64 (29%)
Chemotherapy at recurrence	
No	198 (90%)
Yes	21 (10%)

Survival

Survival outcome for short course radiotherapy is displayed according to prognostic group in Fig. 1. The RTOG prognostic groupings were significantly predictive of outcome in this patient population ($p < 0.001$, log-rank test). Pairs of groups were tested using the log-rank test to detect which individual groups differed significantly from other groups. Groups 4, 5, and 6 were significantly different from each other (5 vs. 6, $p = 0.0178$; 4 vs. 6, $p < 0.001$; 4 vs. 5, $p = 0.0031$, log-rank test). No significant difference could be detected by the log-rank test between Groups 1, 2, and 3 ($p = 0.2560$, log-rank test). However, the combination of 1, 2, and 3 as a whole survived significantly longer when compared to either Group 4, 5, or 6 ($p < 0.001$, log-rank test).

The association of chemotherapy as part of initial treatment with survival was tested. For this population as a whole, chemotherapy was not a predictor of outcome in univariate analysis ($p = 0.1821$, log-rank test). When adjusted for grouping, chemotherapy treatment was a significant predictor of survival ($p = 0.023$, logrank test). Median survival was shorter in those patients receiving chemotherapy in prognostic Groups 1–3, whereas it was longer in those receiving chemotherapy in prognostic Groups 4–6. This difference was only statistically significant in Group 5 where median survival was improved from 196 to 377 days for those who were treated with adjuvant chemotherapy.

Acute toxicity

Of 174 patients for whom information on clinical progress during treatment was available, 12% required increased steroids during treatment, including 3.3% who experienced significant clinical deterioration unresponsive to steroids.

Eleven percent (23) failed to complete radiation. The stated reasons were the refusal of nine patients to continue in view of poor prognosis, eight patients with clinical progression of disease or symptoms, three deaths known to be unrelated to treatment or disease, two deaths of uncertain cause, one patient with a brain abscess, and one patient with no information available. These patients were included in the survival analysis.

Necrosis

Of 13 patients undergoing 15 reoperations and five patients undergoing autopsy at Johns Hopkins Hospital, the radiation necrosis rate was 6% (1 out of 18). The median time from the start of irradiation to autopsy/reoperation was 12 months (range: 3 days to 5.7 years; average: 1.3 years).

DISCUSSION

The value of the prognostic groupings developed by Curran *et al.* (4) have been verified in this patient population. The distribution of patients among the prognostic groups was similar in our study and the RTOG population (Fig. 2). The survival for Groups 4, 5, and 6 differed significantly when compared with each other using the log-rank test. Although the results for Groups 1, 2, and 3 did differ as expected, statistical significance was not demonstrated in our population. This may have been a result of the smaller number of patients in these groups. When Groups 1–3 were combined, their survival did differ significantly from the outcome for each of Groups 4, 5, and 6.

The validation of these prognostic groupings in an additional large group of patients treated by a different regimen is a significant finding. Interpretation of results of malignant glioma treatments has been fraught with difficulty because patient prognostic factors have been more important in predicting outcome than treatment effects

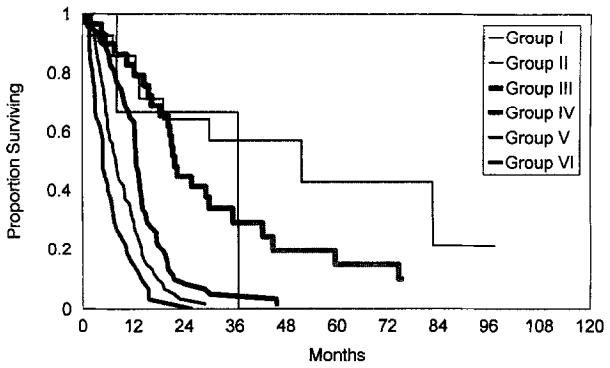

Fig. 1. Proportion of patients surviving after short course radiation therapy. Prognostic groupings as determined by Curran *et al.* (4).

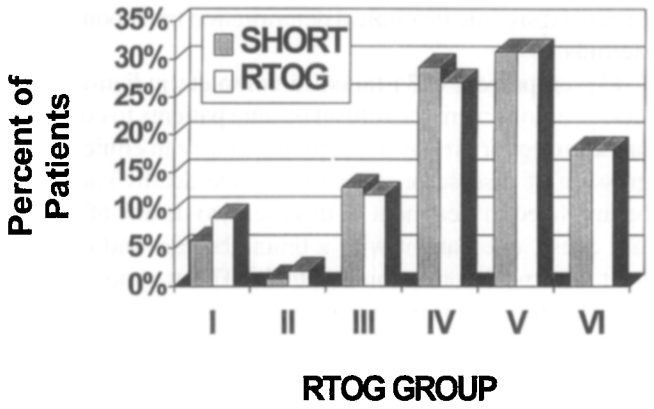

Fig. 2. Percent of patients in each prognostic group in the present study and in the RTOG study.

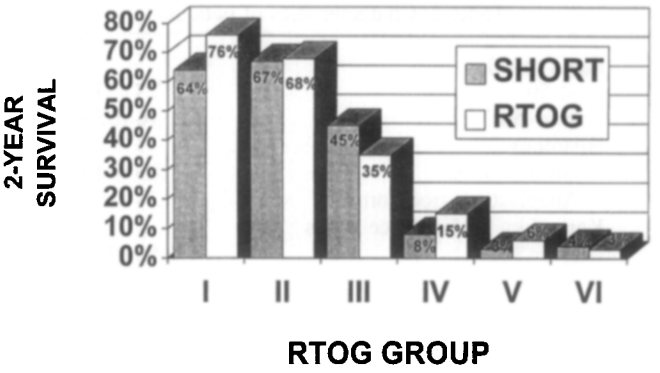

Fig. 4. Percent 2-year survival by prognostic group for patients treated with the short regimen and for the comparison group of RTOG patients. The number in the bars is percent two-year survival.

have been. The use of standardized criteria for assigning patients to accepted prognostic groups allows results of treatment regimens to be more meaningfully compared and also provides clinically useful information about expected outcome that is more relevant to the particular circumstances of individual patients.

The primary objective of this study was to determine whether the survival results of the SHORT regimen are equivalent to more prolonged treatment courses. The survival results seen with the SHORT regimen are similar to the results achieved with aggressive therapy on the combined RTOG protocols for each prognostic group (Figs. 3 and 4). The treatments used in these protocols are summarized in Table 3 (2, 5, 11, 12). As this is an historical comparison, statistical tests of significance were not performed. Survival in our study was measured from the date of surgical procedure, whereas the RTOG measured survival from the date of randomization. Uncertainty about the interval between surgical procedure and randomization may introduce a several week bias in the survival figures; however, this would not substantially alter the similarity of the results.

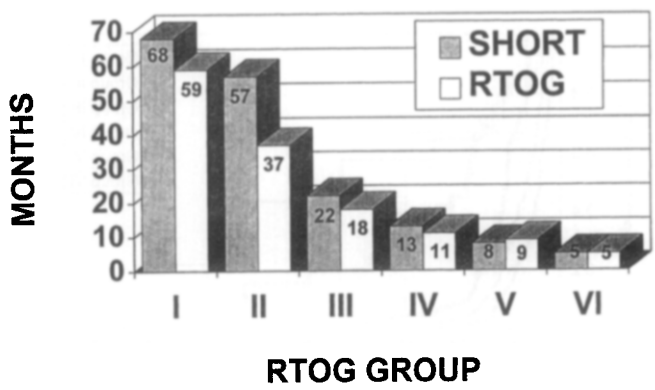

Fig. 3. Median survival by prognostic groups for patients treated by the short regimen and RTOG patients. The number in the bars is the median survival in months.

Other investigators have published the results of short course regimens, but these series have only included small numbers of highly selected patients. Bauman *et al.* (2) have reported the results for 29 patients of age 65 or greater or with KPS $< =$ 50. Survival for those with a KPS $<$ 50 was similar to results of standard treatment, but other patients had a shorter survival with this regimen than would have been expected. Newall *et al.* (13) has described a group of 18 selected patients greater than 60 years old who had a median survival of 11 months after treatment with 30 Gy in 10 fractions.

In our study, a survival benefit could not be clearly demonstrated within each subgroup for those treated with chemotherapy except for a large benefit seen in Group 5. The survival tended to be worse for patients in Groups 1–3 who received chemotherapy, but this may be the result of selection bias. The benefit of standard nitrosourea chemotherapy is known to be modest (2, 15, 16), and is generally demonstrated by an improved number of long-term survivors rather than improved median survival. It would be unlikely that a significant benefit could be seen with the numbers of patients in each subgroup in this study. This is a retrospective study; therefore, the striking benefit seen for chemotherapy-treated patients in Group 5 may very well be the result of selection of more favorable pa-

Table 3. Treatment arms in RTOG studies

Trial	Treatment
74-01	60 Gy whole brain +/− 10 Gy Boost
	60 Gy + carmustine
	60 Gy + semustine + dacarbazine
79-18	60 Gy + carmustine +/− misonidazole
83-02	Radiation twice a day* with carmustine
	64.8–81.6 Gy (1.2 Gy fractions)
	48.0–54.4 Gy (1.6 Gy fractions)

* Dose escalation study.

RTOG = Radiation Therapy Oncology Group. (included in analysis by Curran *et al.*)

tients and/or the fact that more patients were treated with chemotherapy in the later years of the study. Further information about the benefits of chemotherapy regimens for particular subgroups would require randomized trials using prognostic groupings as stratification factors.

The toxicity of the SHORT regimen was acceptable with only 9% of patients requiring increased steroids to remain stable and 3% of patients deteriorating despite increased doses. It is not possible to determine whether clinical progression was the result of tumor progression or a treatment effect. Within the observed survival and follow-up period, the risk of necrosis was within the range expected for conventional radiotherapy (10). Chemotherapy was safely administered in sequence with radiation given by the SHORT regimen.

The SHORT treatment not only reduces the number of visits from 30–33 to 17, a 45–50% reduction, but also adds a 2-week break after 10 treatments. These changes in treatment approach significantly decrease the burden of treatment on patients with short survival time who may also have a decreased performance status resulting in large care needs. This benefit extends not only to the effort and costs involved in transportation, but also reduced time off from work both for those receiving treatment and their caregivers who bring them for radiation treatments. The logistic challenges faced by patients and caregivers, whether employed or not, are likely to be substantially reduced by a regimen requiring 17 visits with a 2-week break rather than a treatment scheme that requires 6–6.5 straight weeks of daily visits. In addition, at our institution the SHORT treatment regimen results in a reduction of billing of approximately $4400, compared to conventional treatment with 30 fractions.

These results demonstrate that the SHORT regimen leads to similar results in unselected patients in prognostic Groups 4–6 compared to RTOG protocol therapy. Although the favorable Groups 1–3 appear to have similar survival results with the SHORT regimen, we are reluctant to consider this regimen to be an appropriate choice for these patients for two reasons. First, the number of patients in these favorable groups in the present study was small. Second, the possibility of increased long-term toxicity such as neurocognitive deficits has not yet been evaluated and may be important in patients with some prospect of longer term survival. Patients in Groups 4–6, who can be appropriately treated with the SHORT regimen, represent the majority of malignant glioma patients. These three groups represent 76% of the patients treated on the RTOG trials and 79% of our patients.

CONCLUSION

Fifty-one Gy in 17 fractions over 5.5 weeks is an appropriate treatment option for patients in RTOG Groups 4–6 who make up the bulk of malignant glioma patients. This treatment substantially reduces the burden of treatment on patients and families, and also reduces hospital costs. Adjuvant chemotherapy can safely be given in sequence with this radiotherapy regimen. Because outcomes do remain poor, eligible patients should continue to be encouraged to enroll in clinical trials. As ever more aggressive treatments are tested, randomized comparisons, including arms with shortened regimens that consider both survival and quality of life as primary endpoints, would provide important information about optimal therapy for this disease. Use of the prognostic groupings developed by the partitioning analysis of the RTOG database as stratification factors in these trials would increase our knowledge about which individual patients have the greatest potential to benefit from new treatments and which might be more appropriately treated with regimens that reduce the number of visits and cost.

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