Purpose: To systematically review the evidence for the use of stereotactic radiosurgery or stereotactic fractionated radiation therapy in adult patients with malignant glioma.

Methods: Key clinical questions to be addressed in this evidence-based review were identified. Outcomes considered were overall survival, quality of life or symptom control, brain tumor control or response and toxicity. MEDLINE (1990–2004 June Week 2), CANCERLIT (1990–2003), CINAHIL (1990–2004 June Week 2), EMBASE (1990–2004 Week 25), and the Cochrane library (2004 issue 2) databases were searched using OVID. In addition, the Physician Data Query clinical trials database, the proceedings of the American Society of Clinical Oncology (1997–2004), ASTRO (1997–2004), and the European Society of Therapeutic Radiology and Oncology (ESTRO) (1997–2003) were searched. Data from the literature search were reviewed and tabulated. This process included an assessment of the level of evidence.

Results: For patients with newly diagnosed malignant glioma, radiosurgery as boost therapy with conventional external beam radiation was examined in one randomized trial, five prospective cohort studies, and seven retrospective series. There is Level I evidence that the use of radiosurgery boost followed by external beam radiotherapy and carmustine (BCNU) does not confer benefit with respect to overall survival, quality of life, or patterns of failure as compared with external beam radiotherapy and BCNU. There is Level I-III evidence of toxicity associated with radiosurgery boost as compared with external beam radiotherapy alone. The results of the prospective and retrospective studies may be influenced by selection bias. Radiosurgery used as salvage for recurrent or progressive malignant glioma after conventional external beam radiotherapy failure was reported in zero randomized trials, three prospective cohort studies, and five retrospective series. The available data are sparse and insufficient to make absolute recommendations. Stereotactic fractionated radiation therapy has been reported as boost therapy with external beam radiotherapy for patients with newly diagnosed malignant glioma in only three prospective studies. As primary therapy alone without conventional external beam radiotherapy for newly diagnosed malignant glioma patients, stereotactic fractionated radiation therapy has been reported in only one prospective study. There were only three prospective series and two retrospective studies reported for patients with recurrent or progressive malignant glioma. Stereotactic fractionated radiation therapy has been reported as boost therapy with external beam radiotherapy and BCNU does not confer benefit in terms of overall survival, local brain control, or quality of life as compared with external beam radiotherapy and BCNU. The use of radiosurgery boost as associated with increased toxicity. For patients with malignant glioma, there is insufficient evidence regarding the benefits/harms of using radiosurgery at the time progression or recurrence. There is also insufficient evidence regarding the benefits/harms in the use of stereotactic fractionated radiation therapy for patients with newly diagnosed or progressive/recurrent malignant glioma. © 2005 American Society for Therapeutic Radiology and Oncology. Published by Elsevier Inc.

Malignant glioma, Stereotactic radiosurgery, Stereotactic fractionated radiation therapy, Evidence-based medicine.

Acknowledgments—The expert panel wishes to express its gratitude to Drs. Jay Loeffler, Roy A. Patchell, Michael A. Vogelbaum, and the members of the American Society for Therapeutic Radiology and Oncology (ASTRO) Health Services Research, Health-care Policy and Economics, and Government Relations Committees for their thoughtful reviews of earlier versions of this evidence-based review. ASTRO wishes to acknowledge McMaster University’s Program in evidence-based Care for carrying out the systematic review used in the development of these recommendations. Further acknowledgments are extended to Alex Chambers (Research Coordinator, Program in Evidence-based Care, McMaster University, Hamilton, Ontario, Canada), and Jennifer Padberg, M.P.H., (Director of Research, ASTRO).

Received May 20, 2005. Accepted for publication May 20, 2005.
INTRODUCTION

As the use of radiosurgery becomes widespread for the management of certain intracranial lesions, the American Society for Therapeutic Radiology and Oncology (ASTRO) Health Services Research Committee concluded that an evidence-based review of the evidence for the use of radiosurgery or fractionated stereotactic radiation therapy in adult patients with malignant glioma would be useful.

Evidence-based medicine

Evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients (1). The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research and patient choice. Systematic research refers to reviews that appraise critically, summarize, and attempt to reconcile the published evidence concerning a particular problem (2). External clinical evidence can inform, but can never replace, individual clinical expertise, and it is this expertise that decides whether the external evidence applies to the individual patient at all and, if so, how it should be integrated into a clinical decision (1).

The final determinant of what treatment should be recommended rests with the oncologist. It is based on his or her clinical impression of the individual case, his or her understanding of the relevant circumstances, and sound medical judgment. ASTRO fully recognizes this and considers adherence to these recommendations voluntary. Rather, this evidence-based review is intended to summarize the current medical literature and identify important questions for further research. These recommendations do not apply to further research in clinical trials.

METHODOLOGY

Expert panel selection

The expert panel was assembled by the Health Services Research Committee of ASTRO and is composed of experts in radiation oncology, physics, clinical research, and outcomes/health services research. A full list of expert panel members is listed in Appendix A (online only). The primary intent was to provide a variety of different perspectives in an attempt to minimize bias (Table 1).

Process overview

In evaluating the evidence regarding the role of radiosurgery or fractionated stereotactic radiation therapy for malignant glioma, a systematic search of the literature was performed. The process included an assessment of the level of evidence (Table 2).

It should be noted that Level I data are not necessarily the ultimate requirement for a proposed treatment to be endorsed as reasonable and necessary. The unique nature of the practice of oncology often precludes the opportunity to perform Level I studies. Many treatments are considered appropriate, in some cases essential, based solely on Level II or Level III data. As previously noted, it is the judgment of the treating physician that ultimately determines which therapy is indicated.

Review of the available data

Pertinent information from the published literature was retrieved and reviewed for the creation of these recommendations. A detailed account of the methods used to obtain this information, including the inclusion/exclusion criteria, databases searched, time periods covered by the search and the search criteria used can be found in Appendix B (online only).

Consensus based on the evidence

The expert panel identified several key clinical questions to be addressed in this review (Appendix B). The expert panel convened on numerous occasions in person and via conference call to discuss and formulate the recommendations. Drafts were developed and circulated in several iterations and all members of the expert panel had an opportunity to comment.

The expert panel did not attempt to codify established practice. The experts reviewed the available evidence and added their best clinical judgment to make final recommendations. The content was peer-reviewed by the ASTRO Health Services Research, Healthcare Policy and Economics, and Government Relations Committees as well as several external reviewers not involved in the development of the document. The ASTRO board of directors reviewed and approved the document before its dissemination.

Revisions/updating

Evidence-based documents are living documents, which reflect the best practice at a particular point and include the most up-to-date evidence available. They require regular revision to cope with changing medical practice, advances in technology, and changes in the environment. This requires commitment to resources to monitor the emerging literature so that decisions as to whether or not a document

<p>| Table 1. Causal pathway: A graphical representation of a “causal pathway” is shown below |
|---------------------------------|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>Patient population</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult patients with malignant glioma</td>
<td>Stereotactic radiosurgery or fractionated stereotactic radiation therapy (as boost after surgery and external beam radiotherapy OR as salvage at the time of relapse after surgery and external beam radiotherapy)</td>
<td>1. Overall survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Quality of life or symptom control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Brain tumor control or response</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Toxicity</td>
</tr>
</tbody>
</table>
should be revised, or if it has become obsolete can be made. Therefore, at regular intervals, this document will be reviewed and a determination made as to whether or not an update should be undertaken, or if the document should be retired.

**RADIOSURGERY OR FRACTIONATED STEREOTACTIC RADIATION THERAPY FOR MALIGNANT GLIOMA**

**Background**

The management of patients with malignant glioma is challenging. Despite best contemporary therapeutic modalities, most patients succumb to their disease. External beam conventional radiation therapy remains the mainstay of management after surgical resection. A dose–response relationship has been reported in earlier studies of postoperative radiation therapy. A randomized trial by the Medical Research Council (4) found an improvement in median survival of 9–12 months when 60 Gy of external beam radiotherapy was compared with 45 Gy. Walker et al. (5) found an increase in median survival from 28 weeks to 42 weeks when external beam radiotherapy doses were increased from 50 to 60 Gy. These data were obtained retrospectively through a review of a series of sequential trials.

For malignant glioma, the majority (90% or more) of recurrences occur within 2 cm of the enhancing edge of the original tumor (6). Furthermore, multicentric or metastatic disease is rare (7). As a consequence, the possibility of escalating the dose to the gross tumor volume (as boost therapy) has been explored through the use of radiosurgery or fractionated stereotactic radiation therapy. In addition, the use of radiosurgery or fractionated stereotactic radiation therapy has been considered at the time of recurrent or progressive malignant glioma after conventional primary treatment.

As the use of radiosurgery or fractionated stereotactic radiation therapy becomes more widespread in the management of malignant glioma, the ASTRO Health Services Research Committee determined that an evidence-based review of this radiation modality was relevant and important. The aim of this evidence-based project was to provide a clear presentation of the key clinical questions related to the use of stereotactic radiosurgery or fractionated stereotactic radiation therapy in the management of malignant glioma and to assess the published evidence for the effectiveness (benefits and harms) of single fraction or fractionated radiosurgery for patients with newly diagnosed or recurrent malignant glioma.

For the purposes of this review, fractionated stereotactic radiation therapy is defined as a highly conformal technique of delivering radiation therapy through the use of a three-dimensional coordinate system to locate intracranial targets precisely. The rationale of fractionation is to spare adjacent normal tissue through radiobiologic concepts. Because of toxicity issues, target sizes with a single fraction of radiosurgery are generally limited to 4 cm or less. Theoretically, fractionated stereotactic radiation therapy may allow for larger targets to be treated safely.

**Results**

There were no studies obtained that examined the use of primary single fraction stereotactic radiosurgery without previous external beam radiotherapy.

Details regarding the studies are summarized in Appendix C, Tables 3–10 (online only). The tables are divided into sections based on study design, whether patients treated were newly diagnosed or recurrent malignant glioma.

The first section reviews the evidence on the use of radiosurgery in either newly diagnosed or recurrent malignant glioma. The next section reviews the evidence on the use of fractionated stereotactic radiation therapy in the management of newly diagnosed or recurrent malignant glioma.

**RADIOSURGERY FOR MALIGNANT GLIOMA (NEWLY DIAGNOSED OR RECURRENT)**

**Boost therapy for newly diagnosed malignant glioma**

**Interpretative summary**

**Key clinical question #1: In patients treated with surgery and conventional radiation, does radiosurgery boost (either before or after conventional radiation) improve survival as compared to no radiosurgery boost in patients diagnosed with malignant glioma?**

Only one randomized trial examined the use of up-front radiosurgery boost to the region of contrast enhancement (<4 cm in diameter) followed by external beam radiotherapy and Bischloroethylnitrosourea (BCNU) compared with external beam radiotherapy and BCNU in selected patients.
with glioblastoma multiforme. These results have been reported in abstract form and the final full report is pending but was made available for our review in preparing this report (8). There was no advantage with radiosurgery boost in terms of survival. The median survival was 13.6 months (95% confidence interval [CI], 11.2–15.2 months) in the external beam and BCNU arm as compared with 13.5 months (95% CI, 11–14.8 months) in the radiosurgery then external beam and BCNU arm \( (p = 0.5711) \). A total of 203 patients were randomly assigned to the two treatment arms in this trial. The study was powered to demonstrate an improvement of 50% in median survival (12.5–18.75 months). Patients were stratified by age and Karnofsky performance status (KPS). A statistically significant difference between treatment arms was not found in the subsets by Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) class III and IV nor in the subset of patients with preoperative tumor size \( \leq 40 \text{ mm} \). Furthermore, a comparison of radiosurgery techniques (gamma knife or linear accelerator) in the arm with radiosurgery boost resulted in no survival difference. However, it was noted that 18% of radiosurgery patients had unacceptable deviations from study protocol. It is unclear whether these patients were treated with a suboptimal radiosurgery technique or were poor candidates for stereotactic radiosurgery because of selection criteria. The extent to which these deviations may have affected outcome remains speculative.

There have been five prospective studies (9–13) reported on the use of radiosurgery boost for newly diagnosed malignant glioma. These were relatively small series ranging from 14 to 37 patients receiving radiosurgery boost. Ages ranged from 5 to 84 years and KPS scores ranged from 20 to 100. The majority of patients had glioblastoma multiforme, although some included patients with anaplastic astrocytoma or mixed glial tumors. Three of the five studies reported no difference in survival as compared with historic expectation, whereas the Loeffler et al. study (10) reported outcomes of 37 patients treated with radiosurgery boost to be better than historic expectation. Mehta et al. (11) reported on the survival of 31 patients who received radiosurgery boost as being superior to historic expectation by RTOG RPA class. For the five studies overall, median survival ranged from approximately 10–26 months for patients with glioblastoma multiforme and approximately 19–28 months for patients with anaplastic astrocytoma.

Seven retrospective studies (14–20) reported on the use of radiosurgery boost for newly diagnosed malignant glioma. The largest was a combined series comprising of three institutions \( (n = 115) \). The smallest series had 11 patients. Ages ranged from 6 to 84 years and KPS ranged from 50 to 100. The majority of patients had Grade 4 glioma, although some anaplastic glioma patients were reported in four (14, 15, 17, 18) of the six studies. One study (16) consisted of only glioblastoma multiforme patients, and one study (15) included lower grade gliomas. Four studies (16–19) reported survivals as being better than historic controls. Overall for the seven retrospective studies, median survivals from diagnosis for glioblastoma multiforme patients ranged from 13 to 25 months.

Although several prospective cohort and retrospective studies have reported survival outcomes of radiosurgery boost after radiotherapy for malignant gliomas to be superior as compared with historical controls, such analyses may be prone to selection bias. Sarkaria et al. (18) and Shrieve et al. (19), for example, compare their results with the results of the RTOG databases. Both studies suggest that radiosurgery boost confers a survival advantage in comparison to the RTOG database stratified by RPA class. Curran et al. (21) analyzed 778 malignant glioma patients enrolled on the RTOG 83-02 trial, a randomized Phase II/III hyperfractionated radiotherapy dose-escalation trial with BCNU chemotherapy. Common stereotactic radiosurgery criteria were applied to these patients, namely: KPS >60, well-circumscribed tumor <4 cm, no subependymal spread, and location not adjacent to the brainstem or optic chiasm. Stereotactic radiosurgery—eligible patients enrolled on RTOG 83-02 had survival superior to that of the stereotactic radiosurgery—ineligible group. The advantage appeared to be due to the selection of a subgroup with a high minimum KPS. Irish et al. (22) also reported on a database of 101 conventionally treated patients with biopsy-proven malignant glioma with known survival times. Twenty-seven percent of patients were deemed eligible for stereotactic radiosurgery. Eligible patients had more favorable prognostic factors and significantly longer median survival than ineligible patients. Radiosurgery eligible, conventionally treated patients with glioblastoma multiforme and a group of radiosurgery-treated patients had similar survival outcomes.

It is important to note, however, that many of the retrospective or cohort studies that indicated an improved survival benefit in patients treated with radiosurgery boost employed radiosurgery at the completion of external beam radiotherapy rather than upfront, as per the RTOG 93-05 protocol (23). This temporal sequence could potentially select out patients who improve or remain stable after completion of external beam radiotherapy. Whether such patients derive a survival benefit from radiosurgery boost after external beam radiotherapy could not be answered by the one randomized trial reported (23).

Furthermore, optimal radiosurgery boost therapy remains to be elucidated. One possible flaw with radiosurgery boost techniques is the use of targeting the visible contrast enhancing lesion. Magnetic resonance spectroscopy studies have documented areas of increased metabolic activity outside the region of contrast enhancement (24). This leaves the possibility that better radiosurgery boost techniques and better patient selection may improve survival as compared to conventionally treated patients who are treated without a radiosurgery boost. In addition, more effective systemic therapeutic agents or radiosensitizers combined with radiosurgery boost may, in theory, improve survival.

**Key clinical question #2: Does the use of radiosurgery boost improve quality of life or symptom control in patients with newly diagnosed malignant glioma?**
The only one randomized trial, RTOG 93-05, (23) reported on no improvement in quality of life (Spitzer index) at baseline compared with the end of therapy in patients treated with radiosurgery boost. There was also no difference in quality-adjusted survival or cognitive decline as measured by the Mini-Intellectual Status Examination. Only two prospective studies commented on KPS score change with radiosurgery boost (11, 13). Mehta et al. (11) reported that median KPS scores increased right after radiosurgery and peaked again 15–18 months after radiosurgery. In Mehta’s study, 14 patients were given external beam radiation followed by radiosurgery, and 15 patients were treated with radiosurgery followed by external beam radiotherapy. Shenouda et al. (12) reported on KPS scores being maintained until 48 weeks when the median KPS dropped to 60 (range, 40–100). Of the six retrospective studies reported, only Shrieve et al. (19) commented on mean KPS outcomes. At diagnosis mean KPS was 91.5 (80–100), which dropped to a mean of 87 (50–100) at last follow-up. In Shrieve’s et al. (19) study, data on 13 patients alive 2 years after diagnosis showed that 62% were no longer taking corticosteroids.

Thus there evidence from one randomized controlled trial that radiosurgery boost before external beam radiotherapy and BCNU does not improve quality of life and cognitive decline. There are some prospective and retrospective studies that report on small patient numbers and KPS outcome. Data on these prospective and retrospective studies are considered insufficient to support a quality of life or symptom control benefit with the use of radiosurgery boost in patients with newly diagnosed malignant glioma. Furthermore, the confounding factor of steroid use and its impact on changes in quality of life or symptom control make interpretation of these outcomes in these studies difficult.

Key clinical question #3: Does the use of radiosurgery boost improve brain control/tumor response in patients with newly diagnosed malignant glioma?

The duration of glioblastoma response to therapy was not reported in the randomized trial RTOG 93-05. However, local failure as a component of failure was seen in 92.5% of all patients. In the prospective study by Gannett et al.(9), the median time to recurrence in radiosurgery boosted patients was 7 months. In the prospective study reported by Mehta et al.(11), the median time to failure was 22 weeks. Shenouda et al. (12) reported 25 weeks as the median time to disease progression. Whereas Mehta et al. (11) and Shenouda’s et al. (12) studies only included Grade 4 astrocytoma, Gannett et al. (9) included some patients with Grade 3 astrocytoma and some patients with mixed glioma histology.

In the retrospective study by Buatti et al. (14), no patient with glioblastoma multiforme had a complete response to radiosurgery boost. The median time to progression for glioblastoma multiforme patients was 3.5 months after radiosurgery. Sarkaria et al. (18), Shrieve et al. (19), and Selch et al. (20) reported on very high local and marginal failures (>80%).

Thus there remains lack of high quality evidence that radiosurgery boost improves brain control or tumor response in patients with newly diagnosed malignant glioma. The prospective and retrospective studies suffer from selection bias and no direct comparisons are made in terms of brain control or tumor response in patients treated with radiosurgery boost vs. not. As such, there is insufficient evidence that radiosurgery boost improves brain control/tumor response in patients with newly diagnosed malignant glioma.

Key clinical question #4: Does the use of radiosurgery boost increase toxicity in patients with newly diagnosed malignant glioma?

Toxicity in the RTOG 93-05 trial (23) was graded using the morbidity scoring scheme by the RTOG and the European Organization for Research in the Treatment of Cancer. For late radiation–related toxicities, there were four Grade 3 late toxicities in the radiosurgery arm compared with none in the external beam and BCNU arm. There were no Grade 4 toxicities related to radiotherapy. Seven patients died from chemotherapy toxicity (5 in the external beam and BCNU arm and 2 in the radiosurgery then external beam radiotherapy and BCNU arm).

For the five prospective cohort studies examining the use of radiosurgery boost in newly diagnosed malignant glioma, toxicity reports range from “no significant acute or late toxicity” to brain necrosis in 2 of 37 patients in the Loeffler et al. series (10) and 4 of 29 patients in the Mehta et al. report (11). The retrospective studies report on a few patients developing significant edema, or radiation necrosis. There is evidence that the addition of radiosurgery boost is associated with an increased risk of toxicity ranging from significant edema to radiation necrosis. Reoperation rates varied from approximately 19–33%. A small proportion of patients subjected to reoperation had necrosis only in the operative specimens retrieved.

Conclusion

There is one randomized controlled trial that provides evidence that the use of radiosurgery boost followed by external beam radiotherapy and BCNU as compared with external beam radiotherapy and BCNU does not confer benefit in terms of overall survival, quality of life, or patterns of failure. There appears to be a slight increased risk of late Grade 3 toxicity with the approach of radiosurgery boost followed by external beam radiotherapy.

The alternative timing strategy of external beam radiotherapy followed by radiosurgery boost has not been reported in a randomized trial setting. Possible areas of research include improved strategies of radiosurgery boost delivery (e.g., targeting using magnetic resonance spectroscopy), better patient selection, improved conformality allowing for safe dose escalation, or novel approaches—for example, combining radiosurgery with systemic agents or molecular targeted approaches. In addition, there is a need for improved quality of life assessments after stereotactic radiosurgery for patients with malignant glioma.
Historically, radiotherapy dose-escalation trials have been conducted with rather ineffective chemotherapy, such as BCNU. At the 2004 American Society of Clinical Oncology meeting, Stupp et al. (25) presented preliminary results of The European Organization for Research and Treatment of Cancer 26981, a Phase III randomized trial evaluating the role of temozolomide chemotherapy concurrent with and also adjuvant after radiotherapy. The median and 2-year survival for the radiotherapy arm was 12.1 months and 10%, in comparison to 14.6 months and 26% (p < 0.0001) for the radiotherapy and temozolomide arm. This is the first clear and categorical prospective randomized evidence supporting the role of chemotherapy in glioblastoma multiforme. Therefore, with a somewhat more effective agent, interest in exploring focal boost techniques such as radiosurgery is rejuvenated. Because radiosurgery is a focal modality that can effectively necrose tumor within the high-dose regions, its major limitation can be speculated to be tumor regrowth from outside the high-dose regions, the zone of poorly defined microscopic spread. If temozolomide can more effectively control the disease in this “peripheral” zone, the impact of enhanced control within the “central” zone could potentially become more meaningful. Hence clinical trials evaluating and testing this hypothesis are being developed and are likely to represent the next generation of studies in this field.

**SALVAGE THERAPY FOR RECURRENT OR PROGRESSIVE MALIGNANT GLIOMA**

**Interpretative summary**

**Key clinical question #1:** Does radiosurgery as salvage for recurrent or progressive malignant glioma improve survival?

There have been no randomized trials comparing radiosurgery for salvage in patients with recurrent malignant glioma as compared with competing interventions such as surgical debulking, chemotherapy, or best supportive care. There have been prospective (26–28) and retrospective studies (15, 29–31) of varying sample sizes ranging from 18 to 132 patients reporting on the use of radiosurgery salvage for patients with recurrent malignant glioma; these demonstrate median survival of 6–12 months. As a point of comparison, Wong et al. (32) reported that the median overall survival of patients with recurrent glioblastoma multiforme (n = 225) or anaplastic astrocytoma (n = 150) treated on Phase II trials of agents presumed to be inactive was 7 months (30 weeks). For glioblastoma patients, only 15% were alive and progression-free at 6 months.

Larson et al. (28) reported on the use of radiosurgery and marimastat in patients with recurrent Grade 3 or 4 astrocytoma. Median survival for these patients were reported as being better than historical controls for Grade 3 astrocytoma patients, but worse for Grade 4 astrocytoma patients. Biases, particularly selection bias contribute to the overall survival estimates in the published series of patients treated with radiosurgery salvage for malignant glioma.

Thus there is insufficient evidence to support a survival benefit in the use of radiosurgery at the time of progressive or recurrent malignant glioma as compared with competing strategies of management such as debulking surgery, chemotherapy, or best supportive care.

**Key clinical question #2:** Does the use of radiosurgery as salvage for recurrent or progressive malignant glioma improve quality of life or symptom control?

None of the studies reported on quality of life or symptom control outcomes.

**Key clinical question #3:** Does the use of radiosurgery salvage improve brain control/tumor response in patients with recurrent or progressive malignant glioma?

Chamberlain et al. (26) reported on 17 patients of whom none had complete response, 8 had partial response, and 9 had stable disease after radiosurgery for salvage. Hall et al. (27) reported that 85% died of local or marginal failure. The median time to progression in Larson’s et al. (28) study was 31 weeks for patients with Grade 3 astrocytoma and 15 weeks for Grade 4 astrocytoma. Sanghavi et al. (30) found a 4-month median progression free survival in 30 patients with recurrent Grade 3 or 4 astrocytoma treated with salvage radiosurgery. Eighty percent of patients in Shrieve et al.’s (31) study experienced either a local or marginal failure with salvage radiosurgery. The results on brain control/tumor response have not been compared with competing strategies such as debulking surgery, chemotherapy, or best supportive care.

**Key clinical question #4:** Does the use of radiosurgery salvage increase toxicity in patients with recurrent or progressive malignant glioma?

The prospective and retrospective studies examining the use of radiosurgery salvage for patients with recurrent or progressive malignant glioma have reported varying degrees of toxicity. Chamberlain et al. (26) found 7/20 patients to have developed early side effects from radiosurgery. One patient had hypersonnolence syndrome 8 weeks after radiosurgery and another patient died of herniation. Nineteen of 86 patients in Shrieve’s et al. report (31) developed radiation necrosis.

**Conclusion**

There is Level II-3 evidence that the use of radiosurgery at the time of recurrence may improve survival and brain control in selected patients but at a cost of possible toxicity. In the absence of higher quality evidence, this intervention may be considered an option for selected patients.

**STEREOTACTIC FRACTIONATED RADIATION THERAPY FOR MALIGNANT GLIOMA**

**Newly diagnosed malignant glioma**

**Interpretative summary**

**Key clinical question #1:** Does the use of fractionated stereotactic radiation therapy for newly diagnosed malignant glioma improve survival?

There has only been one study of fractionated stereotactic radiation therapy used in the primary treatment for malig-
nant glioma (Grade 3 or 4 astrocytoma) (33). This small prospective study (n = 19 patients) found no difference in time to progression or median survival from historical controls.

One additional prospective, multi-institutional Phase II trial of fractionated stereotactic boost combined with external beam radiation, limited only to glioblastoma multiforme patients, has been completed by the RTOG. This trial, RTOG BR-0023, is a Phase II trial of accelerated radiotherapy using weekly stereotactic conformal boosts for supratentorial glioblastoma. This trial examined the use of conventional external beam radiotherapy to a dose of 5000 cGy in 25 daily fractions with stereotactic radiosurgery boost consisting of four treatments of 5 or 7 Gy, once per week during Weeks 3–6. BCNU was given within 1 month after completing radiotherapy for six cycles. Target sample size was 76. Accrual has been completed. Results are pending.

The other four studies (34–37) combined external beam radiotherapy with a fractionated regimen of stereotactic radiation given as boost. All of these studies included astrocytoma Grades 3 and 4; the study by Regine et al. (36) included some low-grade glioma patients in addition to those with malignant glioma.

Baumert et al. (34) reported 1- and 2-year survival rates to be 77% and 42%, respectively. These data were compared to a historical group and were reported as being superior for the fractionated stereotactic radiation therapy group of patients.

Because of heterogeneity, small sample size, and lack of randomized data, it is not possible to discern whether a survival benefit exists with the use of fractionated stereotactic radiation therapy for newly diagnosed malignant glioma patients.

Key clinical question #2: Does the use of fractionated stereotactic radiation therapy for newly diagnosed malignant glioma improve quality of life or symptom control?

None of the studies reported on quality of life or symptom control outcomes.

Key clinical question #3: Does the use of fractionated stereotactic radiation therapy for newly diagnosed malignant glioma improve local brain control or brain tumor response?

Baumert et al. (34) reported on a mean time of 11 months to progression after fractionated stereotactic radiation therapy. Nieder et al. (33) reported that the median time to progression was 5 months in his study with no significant difference as compared with historical controls treated with conventional external beam radiotherapy. Regine et al. (36) reported that the median time to response (at least 20% reduction in the multiple of the cross sectional diameter based on magnetic resonance imaging) was 4 months.

Key clinical question #4: Does the use of fractionated stereotactic radiation therapy for newly diagnosed malignant glioma increase toxicity?

Reported toxicities included reoperation from radiation necrosis in 1 of 17 patients in Baumert’s study (34) to 4 of 12 patients having radionecrosis in Cardinale’s report (35).

Conclusion

Because of the heterogeneity of studies, small sample sizes, and lack of randomized Phase III data, there is insufficient evidence that fractionated stereotactic radiation therapy for newly diagnosed malignant glioma confers benefit in terms of survival, quality of life, symptom control, or local brain control or brain tumor response. As such, fractionated stereotactic radiation therapy for newly diagnosed malignant glioma given as primary therapy after surgery or as boost therapy after conventional external beam radiotherapy remains experimental. Of note, the RTOG has completed a prospective Phase II trial, results of which are currently unavailable.

SALVAGE AT THE TIME OF RECURRENT OR PROGRESSION

Interpretative summary

Key clinical question #1: Does the use of fractionated stereotactic radiation therapy for recurrent or progressive malignant glioma improve survival?

There have been three prospective (38-40) and two retrospective studies (41, 42) that reported the use of fractionated stereotactic radiation therapy for recurrent or progressive malignant glioma. The majority of patients had Grade 4 astrocytoma and a few had progressive Grade 3 glioma or transformed low-grade glioma. Survivals were variable ranging from a median survival of 6.7 to 12 months after stereotactic fractionated radiation therapy. Cho et al. (41) compared the results of 46 patients treated with radiosurgery and 25 patients treated with fractionated stereotactic radiation therapy for progressive malignant glioma. Median survival was not statistically different in those patients receiving radiosurgery salvage as compared with fractionated stereotactic radiation therapy for salvage.

Key clinical question #2: Does the use of fractionated stereotactic radiation therapy for recurrent or progressive malignant glioma improve quality of life or symptom control?

Laing et al. (39) was the only study that reported on symptom control. Seventy-seven percent of patients treated with fractionated stereotactic radiation therapy at recurrence had improved Barthel scores at 3 months, whereas 67% had improved Barthel indices at 6 months. The ability for patients to taper or discontinue steroid use with fractionated stereotactic radiation therapy at the time of recurrence has not been adequately reported.

Key clinical question #3: Does the use of fractionated stereotactic radiation therapy for recurrent or progressive malignant glioma improve brain control or brain tumor response?

Lederman et al. (38) reported that 7.1% of patients...
treated with fractionated stereotactic radiation therapy demonstrated stable disease. No patient demonstrated complete or partial response. Laing et al. (39) reported decreased tumor size in 35% of patients in his series. The majority of patients in the Laing et al. (39) and Cho et al. (41) series had local or marginal failure.

Key clinical question #4: Does the use of fractionated stereotactic radiation therapy for recurrent or progressive malignant glioma result in toxicity?

Laing et al. (39) reported on 4 of 22 patients developing neurologic deterioration due to radiation toxicity. Three of 25 patients in Cho’s et al. (41) series underwent reoperations for radiation necrosis or progression.

Conclusion

Because of the heterogeneity of studies, small sample sizes, and lack of randomized Phase III data, there is insufficient evidence that fractionated stereotactic radiation therapy for recurrent or progressive malignant glioma confers benefit in terms of survival, quality of life, symptom control, or local brain control/brain tumor response as compared with competing strategies such as debulking surgery, chemotherapy, or best supportive care. Also, there is insufficient evidence that fractionated stereotactic radiation therapy provides superior or equivalent benefit in terms of survival, quality of life, symptom control, local brain control/brain tumor response, or toxicity as compared with a single fraction of radiosurgery for recurrent or progressive malignant glioma.

Overall, there is insufficient evidence that fractionated stereotactic radiation therapy for recurrent or progressive malignant glioma confers benefit over competing interventions and should be regarded as experimental.

ONGOING TRIALS

The RTOG is conducting a Phase II trial (BR-0023) of accelerated radiotherapy using weekly stereotactic conformal boosts for supratentorial glioblastoma multiforme. This trial examines the use of conventional external beam radiotherapy to a dose of 5000 cGy in 25 daily fractions with stereotactic radiotherapy boost consisting of four treatments of 5 or 7 Gy, once per week during Weeks 3–6. BCNU is given within 1 month after completion of radiotherapy for six cycles. Target sample size is 76. Accrual has been completed and results are pending.

The European Organization for Research and Treatment of Cancer (22972) and the Medical Research Council (BR10) are conducting a Phase III randomized trial of focal fractionated conformal stereotactic boost following conventional radiotherapy of high-grade gliomas. This study randomizes patients with high-grade gliomas after surgery to partial brain irradiation (54–60 Gy) followed by a fractionated stereotactic boost (4 × 5 Gy daily) or no further treatment. Eligibility criteria include small high-grade gliomas (World Health Organization III/IV) ≤4 cm in diameter, age <65 years, World Health Organization performance status 0–1. The trial was planned requiring 550–600 patients to detect a 10% difference in 2-year survival (34). Results are pending.

Additionally, several single-institution trials are ongoing or planned.

REFERENCES

8. Souhami L. Personal communication; August 2004.
17. Prisco FE, Weltman E, de Hanriot RM, et al. Radiosurgical


