



## **Evidence-based Series #9-3: Section 1**

# **Radiotherapy for Newly Diagnosed Malignant Glioma in Adults: A Clinical Practice Guideline**

*N. Laperriere, J. Perry, L. Zuraw, and members of the Neuro-oncology Disease Site Group*

A Quality Initiative of the  
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)  
Developed by the Neuro-oncology Disease Site Group

**Original Report Date: September 19, 2000**

**Current Report Date: November 2, 2005**

### **Questions**

What is the role of radiotherapy in adult patients with newly diagnosed malignant glioma? If radiotherapy is offered, what are the optimal radiotherapy characteristics?

### **Target Population**

These recommendations apply to newly diagnosed adults with histologic confirmation of the following diagnoses: glioblastoma multiforme, malignant astrocytoma, malignant astrocytoma grade 3, malignant astrocytoma grade 4, malignant glioma, or gliosarcoma.

### **Recommendations**

- Postoperative external beam radiotherapy is recommended as standard therapy.
- The high-dose volume should incorporate the enhancing tumour plus a limited margin (e.g., 2 cm) for the planning target volume, and the total dose delivered should be 60 Gy in 2 Gy fractions, with concurrent temozolomide at 75 mg/m<sup>2</sup>.
- Radiation dose intensification and radiation sensitizer approaches are not recommended as standard care.

### **Qualifying Statements**

- A randomized study has established the equivalence of 60 Gy in 30 fractions to 40 Gy in 15 fractions in older patients (≥60 years).
- Since the outcome following conventional radiotherapy is so poor in older patients with a poor performance status, supportive care alone is a reasonable therapeutic option in those patients.

### **Key Evidence**

- Five of six randomized studies demonstrated that postoperative radiotherapy improves survival compared with no radiation in patients with malignant glioma.
- Seven of eight randomized studies of hyperfractionated versus conventionally fractionated radiotherapy demonstrated no significant survival benefit of hyperfractionated radiotherapy. No randomized trials have examined survival following doses in the 50–60 Gy range.

- A high-dose volume incorporating the enhancing tumour plus a limited margin (e.g., 2 cm) has achieved similar survival to volumes incorporating whole brain for part or all of the treatment in two randomized studies.
- Radiation dose intensification and radiation sensitizer approaches have not demonstrated survival rates superior to those seen with conventionally fractionated doses of 50-60 Gy in randomized studies.
- Two randomized studies demonstrated that concurrent and adjuvant administration of temozolomide with radiotherapy improves survival compared to radiotherapy alone in patients with glioblastoma.

### Future Research

- In view of the poor results with conventional radiotherapy in this disease, patients should be encouraged to participate in properly conducted experimental studies.
- It is strongly recommended that future studies in patients with brain tumours include measures of toxicity and quality of life.

### Related Guidelines

- Practice Guideline Initiative Practice Guideline Report #9-2 *Adjuvant Systemic Chemotherapy, Following Surgery and External Beam Radiotherapy, for Adults with Newly Diagnosed Malignant Glioma.*

#### *Funding*

The Program in Evidence-based care is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

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## **Evidence-based Series #9-3: Section 2**

# **Radiotherapy for Newly Diagnosed Malignant Glioma in Adults: A Systematic Review**

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A Quality Initiative of the  
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)  
Developed by the Neuro-oncology Disease Site Group

**Original Report Date: September 19, 2000**

**Current Report Date: November 2, 2005**

### **QUESTIONS**

What is the role of radiotherapy in adult patients with newly diagnosed malignant glioma? If radiotherapy is offered, what are the optimal radiotherapy characteristics?

### **INTRODUCTION**

Malignant gliomas are the most common primary brain tumour in adults, occurring at a rate of five cases per 100,000 per year. Subsequent to the performance of optimal surgical resection or biopsy, radiotherapy is the dominant form of therapy administered postoperatively. Unlike with many other malignancies, recurrences occur predominantly locally, with very few patients recurring either via cerebrospinal fluid (CSF) pathways or with metastases outside the central nervous system. This pattern of local recurrence has led to the study of ways of intensifying the radiation dose in an effort to improve local control rates, and, thereby, survival in a disease that in most cases is fatal.

Between 1982 and 1994, there were 3,279 cases of glioblastoma recorded in the Ontario Cancer Registry (1). That same survey documented regional variations in the dose of radiotherapy administered in this patient population. In addition, the last three decades have seen a large volume of published studies on the use of radiotherapy in the treatment of this illness. Accordingly, the Neuro-oncology Disease Site Group felt it was timely to examine the data available and make recommendations for optimal standard radiotherapy for these patients.

This guideline is limited to radiation therapy issues. Patients with newly diagnosed malignant glioma can also receive chemotherapy, and that modality has been used in the control arms of some of the trials included in this guideline. The Neuro-oncology Disease Site Group is preparing a separate guideline on chemotherapy in this patient population. Eventually that guideline and this one on radiotherapy will be consolidated into a single guideline. Until then, please refer to the companion guideline on adjuvant systemic chemotherapy, following surgery and external beam radiotherapy, for adults with newly diagnosed malignant glioma (Practice Guideline Report #9-2).

## **METHODS**

This systematic review was developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC). Evidence was selected and reviewed by three members of the PEBC Neuro-oncology Disease Site Group and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on radiotherapy for newly diagnosed malignant glioma. The body of evidence in this review is primarily comprised of mature randomized controlled trial data. This evidence forms the basis of a clinical practice guideline developed by the Neuro-oncology DSG. The systematic review and companion guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

### **Literature Search Strategy**

MEDLINE (1966 to October 2005), CANCERLIT (1983 to October 2002), and the Cochrane Library (2005, Issue 4) databases were searched with no language restrictions. "Glioma" (Medical subject heading [MeSH]) was combined with "radiotherapy" (MeSH), "radiotherapy dosage" (MeSH), "dose fractionation" (MeSH), "brachytherapy" (MeSH), "radiation-sensitizing agents" (MeSH), "radiosurgery" (MeSH), and each of the following phrases used as text words: "hypofraction:", "hyperfraction:", "accelerated", "particle". These terms were then combined with the search terms for the following study designs or publication types: practice guidelines, meta-analyses, and randomized controlled trials. To identify non-randomized studies when no randomized trials were available, the search was repeated using all search terms except the study design terms described above. A search of the proceedings of the 1997 through 2005 meetings of the American Society of Clinical Oncology (ASCO) and the 1998 to 2004 meetings of American Society for Therapeutic Radiology and Oncology (ASTRO) was also conducted. Relevant articles and abstracts were reviewed and the reference lists from these sources were searched for additional trials.

### **Inclusion Criteria**

Articles were selected for inclusion in this systematic review of the evidence according to the following criteria:

1. They were meta-analyses and randomized trials comparing various aspects of radiotherapy in patients with malignant glioma.
2. Where no randomized trials were available, non-randomized studies were reviewed.
3. Abstracts of trials were also considered.
4. The outcome of interest was survival.

### **Synthesizing the Evidence**

One-year mortality data from the trials of postoperative radiotherapy versus no postoperative radiotherapy, and the trials of hyperfractionated radiotherapy versus conventional fractionation radiotherapy, were pooled in separate meta-analyses using the software package Metaanalyst<sup>0.998</sup> (J. Lau, Boston, MA, USA). Reported figures or estimates obtained from tables or graphs were used. For the calculation of survival, the total randomized population was included in the denominator, based on intention-to-treat, unless the only available data were for the evaluable patients. The random effects method was used as the more conservative estimate of effect (2). The pooled results were examined for statistically significant heterogeneity ( $p < 0.10$ ). Results were expressed as risk ratios (RR), where an RR less than 1.0 favours the experimental group, and an RR greater than 1.0 favours the control group.

**RESULTS**

**Literature Search Results**

The literature search identified 47 randomized trials. All studies reviewed (randomized trials and other studies) are listed in Table 1. Seven randomized trials compared conventional radiation with no radiation. In addition, four randomized trials examined the issue of radiation volume and radiation dose. Seven randomized trials and one published meta-analysis compared hyperfractionated radiotherapy with conventional radiotherapy. There was also one randomized trial of hyperfractionation comparing different radiation doses. One randomized trial of accelerated radiotherapy, three randomized trials of hypofractionation, three randomized trials of brachytherapy, one randomized trial of hyperthermia, and five randomized trials of particle therapy were also reviewed. Fifteen randomized trials and two published meta-analyses of sensitized radiation were found. Two of those trials compared concurrent and adjuvant temozolomide with radiotherapy to radiotherapy alone. One randomized controlled trial (RCT) compared stereotactic radiosurgery with radiotherapy and carmustine (BCNU) to radiotherapy and BCNU alone.

**Table 1. Studies eligible for inclusion in this report.**

Treatment	Number of Studies	Reference Numbers	Summary of Results
Conventional radiation versus no radiation	6	3-8	Table 2
Radiation volume	2	9-10	Page 5
Radiation dose	2	11-12	Page 5
Hyperfractionated radiotherapy	8 + 1 meta-analysis	13-21	Table 3
Accelerated radiotherapy	5	22-26	Page 8
Hypofractionated radiotherapy	9	27-35	Page 9
Brachytherapy	3	36-38	Page 9
Hyperthermia	1	39	Page 10
Particle therapy	5	40-44	Table 4
Sensitized radiation	15 + 2 meta-analyses	45-59	Table 5
Radiosurgery	12	60-71	Page 13

**Outcomes**

***Conventional Radiation Versus No Radiation***

Table 2 presents the results from six randomized trials where one of the arms contained no postoperative radiotherapy and one of the arms contained postoperative conventionally fractionated external beam radiotherapy with or without chemotherapy (3-8). Patients in one trial were randomized according to birth date (4). In the other trials, the randomization procedure was acceptable (5,6) or not described (3,7,8). Three patients withdrew from the trial by Shapiro et al (3), and 11 patients in the trial by Andersen (4) did not receive any radiotherapy due to poor general condition or operative death. There were a large number of protocol violations (19% to 27%) in three trials (5,6,8), two of which included results for both the total randomized population and the “valid study group” (i.e., excluding the protocol violations) (6,8). Kristiansen et al (7) did not provide information on protocol violations or number of patients lost to follow-up. Of note, the chemotherapy used in the trial by Sandberg-Wollheim et al (8) was PVC (procarbazine, vincristine, and lomustine).

Five of the six trials demonstrated a statistically significant survival benefit for postoperative radiotherapy compared with supportive care only or single- or multi-agent chemotherapy without radiation. There was an imbalance of prognostic factors in the one negative study (3). In that study, the mean Karnofsky performance status (KPS) for the no-radiation arm was 71% versus 57% for the radiotherapy arm ( $p < 0.05$ ). That imbalance in a major prognostic factor and the small number of patients could explain the lack of a statistically significant survival benefit from postoperative radiotherapy in that study. The remaining five trials, which were positive, had larger numbers of randomized patients, and the study arms were balanced with respect to the major prognostic factors of age and KPS at baseline. Analyses of both the total randomized population and the “valid study group” by Walker et al (6) demonstrated a significant survival benefit for postoperative radiotherapy. Only a nonsignificant trend towards improved survival was found when Sandberg-Wollheim et al (8) analyzed the 139 patients in the “valid study group” (median, 66 months for postoperative radiotherapy with or without chemotherapy versus 47 months for chemotherapy alone;  $p = 0.091$ ), although this may be due to fewer patients in the analysis.

Figure 1 illustrates the results of pooling the six randomized trials of postoperative radiotherapy versus no postoperative radiotherapy. There was a statistically significant survival benefit favouring postoperative radiotherapy compared with no radiation (RR, 0.81; 95% confidence interval [CI], 0.74 to 0.88;  $p < 0.00001$ ). There was no significant heterogeneity ( $X^2 = 6.73$ ,  $p > 0.10$ ).

**Table 2. Randomized studies of postoperative radiation compared with no radiotherapy in malignant glioma.**

Study (Reference)	Study Group	Radiation Dose Gy/# Fractions	# Patients Randomized (Analyzed)	Median Survival (weeks)	p value
Shapiro, 1976 (3)	CT RT+CT	- 60	16 (16) 17 (17)	30 44.5	NR not significant
Andersen, 1978 (4)	Surgery alone RT	- 45/25	57 (57) 51 (51)	15* 23*	$p < 0.005$ survival at 6 months
Walker, 1978 (5) ‡	Surgery alone RT	- 50-60/25-35	42 (31) 93 (68)	14† 36†	$p = 0.001$
Walker, 1980 (6) ‡	CT RT	- 60/30-35	111 (111) 118 (118)	31 37	$p = 0.003$
Kristiansen, 1981 (7) ‡	Surgery alone RT +/- CT	- 45/25	38 (38) 80 (80)	23 47	NR significant
Sandberg-Wollheim, 1991 (8)	CT RT+CT	- 58/27	87 (87) 84 (84)	42 62	$p = 0.028$

Note: CT, chemotherapy; NR, not reported; RT, radiotherapy.

\*Calculated from survival curve.

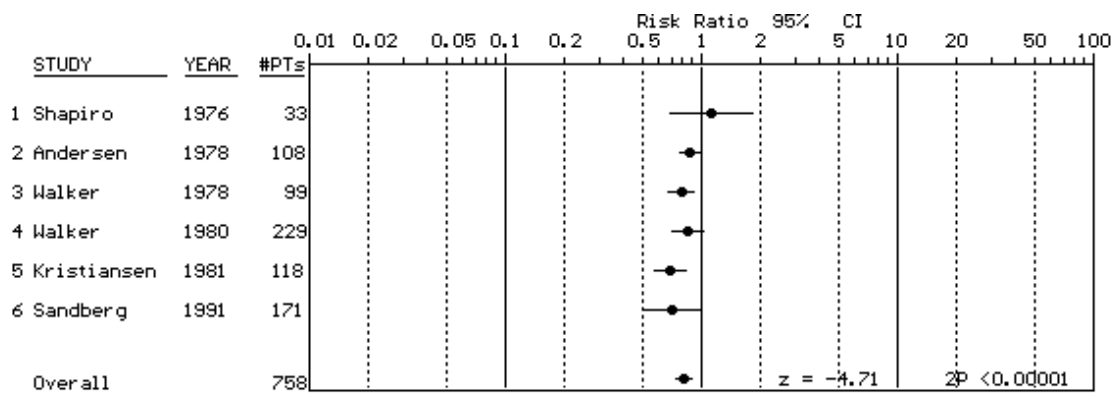
†Only results for the evaluable patients were reported (31 patients in the surgery alone arm and 68 patients in the RT arm).

‡Multi-arm study that included a radiation alone arm and a radiation plus chemotherapy arm. For both studies by Walker et al (5,6), only data from the radiation alone arm are shown in Table 2. Kristiansen et al (7) reported combined data from the radiation alone arm and the radiation plus chemotherapy arm. In each of these studies, there was a significant survival benefit favouring radiation plus chemotherapy compared with no radiotherapy but no significant difference in survival between radiation alone and radiation plus chemotherapy (data not shown).

**Figure 1. Pooled results of trials of postoperative radiotherapy (RT) versus no radiotherapy.**

Study	Postoperative Radiotherapy		No Postoperative Radiotherapy		Risk Ratio for 1-year Mortality (Random Effects)	95% Confidence Interval	
	Deaths	Total	Deaths	Total		Low	High
Shapiro, 1976 (3)	12	17	10	16	1.13	0.69	1.84
Andersen, 1978 (4)	44	51	57	57	0.86	0.77	0.97
Walker, 1978* (5)	52	68	30	31	0.79	0.68	0.92
Walker, 1980 (6)	74	118	82	111	0.85	0.71	1.01
Kristiansen, 1981 (7)	51	80	35	38	0.69	0.57	0.84
Sandberg-Wollheim, 1991 (8)	34	84	50	87	0.70	0.51	0.97
<b>TOTAL</b>	<b>267</b>	<b>418</b>	<b>264</b>	<b>340</b>	<b>0.81</b>	<b>0.74</b>	<b>0.88</b>

\* Only results for the evaluable patients were reported.



Favours Postoperative RT  $\approx$  Favours No Postoperative RT  
 overall risk ratio = 0.81 (95% CI, 0.74 to 0.88;  $p < 0.00001$ )

**Radiation Volume**

Before the computed tomography and magnetic resonance imaging era, many reports on the management of malignant glioma employed whole brain irradiation. However, the last 20 years have seen a definite shift away from utilizing whole brain fields to the use of regional fields with margins around enhancing disease of the order of 2 cm. This was in part due to the better tumour localization associated with computerized tomography (CT) and magnetic resonance imaging (MRI), the many reports documenting that the primary cause of treatment failure was related to tumour recurrence at the original site in over 90% of cases, and the wish to reduce radiation-related morbidity associated with whole brain irradiation (72,73). Initially, lateral opposed parallel pairs were utilized to deliver the regional radiation fields, but increasingly, with the advent of conformal radiotherapy, more conformal radiation plans with the use of multiple non-coplanar fields are being utilized.

There have been two randomized trials investigating the issue of radiation volume. Shapiro et al reported the results of the Brain Tumor Cooperative Trial 8001 where 571 patients were randomized to three different chemotherapy regimens (9). Patients accrued in 1980 and 1981 received 6020 cGy whole brain radiation, whereas patients accrued in 1982 and 1983 were randomly assigned to receive either whole brain radiation or 4300 cGy whole-brain radiation plus a boost of 1720 cGy coned down to the pre-radiation-enhancing tumour volume plus a 2 cm margin with the dose prescribed to the 90% isodose contour. There were no statistically significant differences in survival among the three chemotherapy arms and no differences in survival among the three different cohorts of radiation volumes.

Kita et al randomly assigned 23 patients to receive 40 Gy in 20 fractions to whole brain followed with a boost of 18 Gy in nine fractions for a total of 58 Gy in 29 fractions and 26 patients to receive 56 Gy in 28 fractions via local fields (10). The survival rates for the whole-brain group versus the local-field boost group were 43% versus 39% at two years and 17% versus 27% at four years, respectively (p-values not reported). The differences in survival rates between the treatment groups were not statistically significant.

### ***Radiation Dose Via External Conventionally Fractionated Radiotherapy***

A Medical Research Council (UK) randomized trial compared 45 Gy in 20 fractions to 60 Gy in 30 fractions in 443 patients (11). Patients were randomized in a 2:1 ratio to the 60 Gy arm to gain more experience with the higher dose and allow a more precise estimate of its effect. At 12 months, the survival rates for the 45 Gy and 60 Gy arms were 29% and 39%, respectively, and the corresponding rates at 18 months were 11% and 18%. That difference was statistically significant ( $p=0.04$ ) and corresponded to an improvement in median survival of two months in the 60 Gy arm. There was a slight imbalance of age distribution in favour of the 45 Gy arm, and, when this was corrected using a proportional hazards regression model, there was an estimated three-month improvement in median survival for 60 Gy ( $p=0.007$ ).

Nelson et al reported on a joint study of the Radiation Therapy Oncology Group (RTOG) and the Eastern Cooperative Oncology Group (ECOG), which involved 626 patients randomized to four study arms: 1) 60 Gy to the whole brain (141 patients); 2) 60 Gy to the whole brain plus a 10 Gy boost to the tumour (103 patients); 3) 60 Gy plus carmustine (156 patients); 4) 60 Gy plus semustine and dacarbazine (138 patients) (12). There were no statistically significant differences in survival among any of the four arms. The median survival times for the 60 Gy and 70 Gy arms were 9.3 months and 8.2 months, respectively.

### ***Hyperfractionated Radiotherapy***

Hyperfractionation involves the use of a larger number of smaller-sized fractions to a total dose that is higher than with conventionally administered irradiation in the same overall treatment time. Normal glial and vascular cells limit the total amount of irradiation that can be administered. Those cells divide very slowly, and are better able to repair sub-lethal damage than neoplastic cells. Consequently, there might be an advantage to administering multiple smaller-sized fractions to a higher total dose, the theory being that the improved repair of sub-lethal damage at lower sized fractions might allow a higher total dose to be associated with the same degree of late sequelae. Neoplastic cells are relatively rapidly dividing cells, and the increased number of daily fractions would increase the chance of radiating them at a more sensitive phase of their cell cycle. At smaller radiation doses per fraction, cell killing is less dependent on oxygen, which might be advantageous given the known areas of hypoxia in these tumours.

Table 3 shows the results of seven randomized studies of hyperfractionated radiotherapy compared with conventionally fractionated radiotherapy (13-18,21). One trial compared treatment with accelerated hyperfractionated radiotherapy with or without difluoromethylornithine (DFMO) to standard fractionated radiotherapy with or without DFMO (21). All the studies were negative except one study by Shin et al where a survival advantage was found for the hyperfractionated arm (15). That study had a small number of patients per arm, and the median survival of 27 weeks for the conventionally fractionated arm was significantly worse than all other published data for conventionally fractionated radiotherapy. The earlier study by Shin et al also showed a trend in favour of the hyperfractionated arm, but there was a statistically significant imbalance in age distribution between the randomized arms favouring the hyperfractionated arm (14). The largest study on hyperfractionation reported by Scott et al clearly showed no benefit for the use of hyperfractionated radiotherapy in malignant gliomas (18). The experimental arm of 72 Gy in 60 fractions arose as the best arm from a randomized

study reported by Nelson et al, which looked at four different hyperfractionated arms to total doses of 64.8, 72.0, 76.8, and 81.6 Gy (19).

Stuschke and Thames (20) pooled data from three randomized trials of hyperfractionation compared with conventional radiotherapy (14,17,74). The pooled results detected a significant survival benefit favouring hyperfractionation (odds ratio [OR], 0.67; 95% CI, 0.48 to 0.93;  $p=0.02$ ). To identify the three trials included in that meta-analysis, MEDLINE and CANCELIT were searched from 1980 to 1995. The search missed the trial by Ludgate et al (16) and an updated report by Shin et al in 1985 (15) on the trial by Fulton et al (74). Stuschke and Thames (20) reported their selection criteria, and they noted that the trial by Payne et al (13) was excluded from their meta-analysis because there was no planned break of more than 14 days in the treatment arms. Some methodological weaknesses in the trial by Fulton et al (74) were identified when study quality was assessed by Stuschke and Thames (20). Specifically, nine of 42 patients in the hyperfractionated radiotherapy arm of the three-arm trial by Fulton et al (74) were sequentially treated after the conventional radiotherapy arm was closed, and there was a slight imbalance in prognostic factors among the treatment arms.

A pooled analysis was conducted for this systematic review that incorporated the additional evidence (13,15) as well as the trials by Shin et al (14) and Deutsch et al (17). The results demonstrated no statistically significant survival benefit for hyperfractionated radiotherapy compared with conventional radiotherapy (RR, 0.89; 95% CI, 0.73 to 1.09;  $p=0.27$ ) (Figure 2). There was no statistically significant heterogeneity ( $X^2=6.27$ ,  $p=0.10$ ). The pooled results are consistent with the negative results of the largest study on hyperfractionation reported by Scott et al in abstract form (18). That trial involved 712 randomized patients, and the overall and subgroup analyses demonstrated no significant difference in median survival for hyperfractionated radiotherapy compared with conventional radiotherapy. The trial could not be included in the pooled analysis because the one-year survival rates and the number of patients randomized to each treatment group were not reported. The trial by Ludgate et al (16) could not be included either because the survival curves were shown for three different age groups rather than for the total study group. The trial by Prados et al (21) could not be included because one-year survival rates were not clear from the survival curves.

**Table 3. Randomized studies of hyperfractionated radiotherapy compared with conventionally fractionated radiotherapy in malignant glioma.**

Study (Reference)	Hyperfractionated Radiotherapy		Conventional Radiotherapy		p value
	Fractionation Time # Patients Randomized (Analyzed)	Median Survival (weeks)	Fractionation Time # Patients Randomized (Analyzed)	Median Survival (weeks)	
Payne, 1982 (13)	36-40 Gy/36-40 2 weeks n=NR (78)†	48‡	50 Gy/25 5 weeks n=NR (79)†	48‡	NR not significant
Shin, 1983 (14)	50 Gy/50 4 weeks n=35 (35)	56	50 Gy/25 5 weeks n=34 (34)	39	NR not significant
Shin, 1985* (15)	6141 cGy/69 4.5 weeks n=43 (43)	39	5800 cGy/30 6 weeks n=38 (38)	27	p=0.007
Ludgate, 1988 (16)	4760 cGy/63 + 1000 cGy/5 5 weeks n=42 (42)	46	4000 cGy/20 + 1000 cGy/5 5 weeks n=34 (34)	32	NR not significant
Deutsch, 1989* (17)	6600 cGy/60 6 weeks n=154 (154)	45§	6000 cGy/30-35 6-7 weeks n=152 (152)	43§	NR not significant
Scott, 1998* (18) n=520 evaluable glioblastoma n=107 evaluable anaplastic astrocytoma	7200 cGy/60 6 weeks NR//	44	6000 cGy/30 6 weeks NR//	49	p=0.44
	7200 cGy/60 6 weeks NR//	189	6000 cGy/30 6 weeks NR//	215	p=0.81
Prados, 2001 (21)	7040 cGy/44 4.5 weeks n=114 ¶	41	5940 cGy/33 6.5 weeks n=117 ¶	42	P=0.75

Note: NR, not reported.

\* Both arms of these studies received BCNU.

† The number of patients randomized per treatment group was not reported, but a total of 168 patients were randomized.

‡ Refers to overall median survival because results were not reported separately by treatment group.

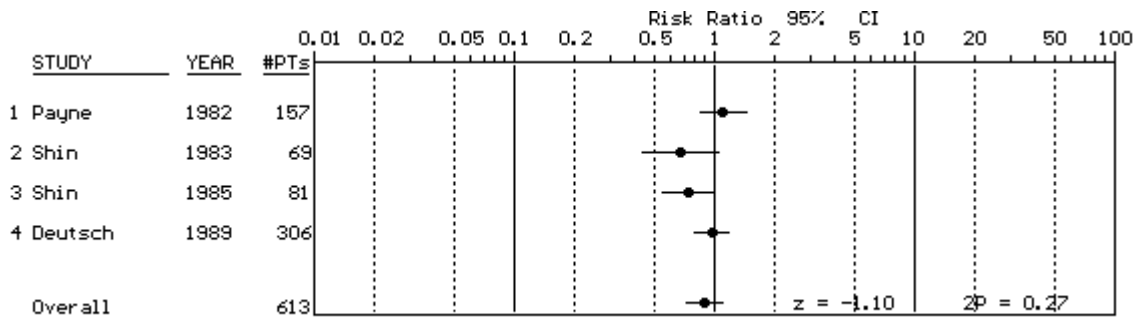
§ Median survival was reported for the evaluable patients (142 patients in the hyperfractionated radiotherapy arm and 140 patients in the conventional radiotherapy arm). The survival curve for the total randomized population showed a median survival of approximately 43 weeks for each treatment group.

// The number of patients randomized per treatment group was not reported, but a total of 712 patients were randomized. Results were reported for evaluable patients by type of malignant glioma.

¶ Half of the patients in each arm received difluoromethylornithine (DFMO)

**Figure 2. Pooled results of trials of hyperfractionated radiotherapy (RT) versus conventional fractionation radiotherapy.**

Study	Hyperfractionated Radiotherapy		Conventional Radiotherapy		Risk Ratio for 1-year Mortality (Random Effects)	95% Confidence Interval	
	Deaths	Total	Deaths	Total		Low	High
Payne, 1982	48	78	44	79	1.10	0.85	1.44
Shin, 1983	16	35	23	34	0.68	0.44	1.04
Shin, 1985	25	43	30	38	0.74	0.54	1.00
Deutsch, 1989	86	154	87	152	0.98	0.80	1.19
TOTAL	175	310	184	303	0.89	0.73	1.09



Favours Hyperfractionated RT  $\approx$  Favours Conventional RT  
 overall risk ratio = 0.89 (95% CI, 0.73 to 1.09; p=0.27)

**Accelerated Radiotherapy**

The aim of accelerated fractionation is to reduce overall treatment time in an effort to reduce the possibility of tumour repopulation during treatment. This is achieved by delivering two or three fractions per day with normal sized fractions.

Accelerated fractionation has been evaluated in a randomized study conducted by the European Organization for Research on Treatment of Cancer (EORTC) (22). In protocol 22803, 340 patients were randomly assigned to conventional radiotherapy or accelerated fractionation with or without misonidazole. Accelerated fractionation consisted of three fractions of 2 Gy per day with a four-hour gap between fractions to deliver 30 Gy in one week. That treatment course was repeated after a two-week break for a total of 60 Gy in 30 fractions in four weeks. There was no difference in survival among the three treatment groups (p-value not reported) and no increased toxicity with accelerated radiation.

In a randomized phase I/II dose escalation study (RTOG 83-02), a subgroup of 305 patients were administered 1.6 Gy twice daily to total doses of 48 or 54.4 Gy (23). The results demonstrated no significant survival difference among all dose schemes (p=0.598), and there was a low toxicity rate with accelerated fractionation.

Brada et al reported a single-arm study of accelerated radiation in 211 patients with malignant astrocytomas (24). Radiation treatment consisted of 55 Gy in 34 fractions (twice daily) delivered to the enhancing tumour and a 3 cm margin. Median survival was 10 months, which was similar to a matched cohort of patients who had received 60 Gy in 30 fractions over six weeks.

Two other small studies also found no improvement in survival or increased toxicity with accelerated fractionation schemes in malignant glioma (25,26). One study evaluated 40 Gy in 20 fractions in one week as part of a randomized phase II study (25), while the other evaluated 60 Gy in 16 days using a single-arm phase II design (26).

### **Hypofractionation**

Hypofractionation refers to the use of a fewer number of larger-sized radiation fractions in an effort to reduce the overall treatment time. As radiotherapy is not curative and survival is relatively short, a hypofractionated schedule that would yield the same survival as more conventionally fractionated regimes with equivalent toxicity would be a useful advance in the management of patients being treated.

There have been several small single-arm prospective studies where hypofractionated radiotherapy was used in patients with prognostic factors that would predict for a shorter survival (i.e., older age and poor performance status) (27-31). The number of patients involved in those studies ranged from 25 to 38. The age criteria varied between greater than or equal to 65 to 70 years, and the Karnofsky Performance Status was generally less than or equal to 50. The following radiation schemes were used: 30 Gy in six fractions, 30 Gy in 10 fractions, 36 Gy in 12 fractions, 37.5 Gy in 15 fractions, and 42 Gy in 14 fractions. Median survival ranged from 4 to 8 months. The authors reported that those results were equivalent to what would have been expected with conventional radiotherapy for the distribution of prognostic factors in those patients, but Bauman et al cautioned that elderly patients with a higher pretreatment KPS (> 50) might benefit from a higher dose radiotherapy regimen (28).

Kleinberg et al reported a study of 219 patients treated with 51 Gy in 17 fractions (32). Patients were retrospectively assigned to six prognostic groups previously identified in a recursive partitioning analysis of the RTOG (75). The six RTOG prognostic groupings were significantly predictive of outcome for patients treated with that shortened regimen (logrank  $p < 0.001$ ). The median survival times for the patients by RTOG groups 1-6 were 68, 57, 22, 13, eight, and five months, respectively. Two-year survival rates were 64%, 67%, 45%, 8%, 3%, and 3%, respectively. 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. Kleinberg et al concluded that 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. The authors cautioned that they 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 neuro-cognitive assessment is lacking on this hypofractionation scheme.

Glinski reported a randomized study in 108 patients comparing 50 Gy in 25 fractions to the whole brain versus a hypofractionated regimen consisting of three separate courses of treatment separated by one-month intervals (33). The first two courses of hypofractionated radiation were 20 Gy in five fractions to the whole brain, while the third course was a 10 Gy boost to the local tumour in five fractions. An analysis of all 108 randomized patients demonstrated no significant difference in survival between the treatment arms, but there was a significant survival benefit favouring hypofractionated radiation compared with conventional radiation in the subgroup of 44 patients with glioblastoma (23% versus 10% at two years;  $p < 0.05$ ).

Two RCTs have been identified that compared dosages of radiation therapy in older patient populations (34,35). A Canadian study by Roa et al (34) randomized 100 patients 60 years or older with glioblastoma multiforme to receive either standard radiation therapy (60 Gy in 30 fractions) or a shorter course of radiation therapy (40 Gy in 15 fractions). The overall survival between the groups was not significantly different: 5.1 months for the patients receiving standard radiation therapy compared to 5.6 months for the patients receiving the shorter course ( $p = 0.57$ ). Initially, the study was designed to measure quality of life; however, the questionnaire used to measure quality of life did not work well with the patient population because of the short survival times. The questionnaire was to be completed prior to treatment, three weeks after starting the treatment, at the completion of the treatment and then at three months intervals thereafter. Unfortunately, 12 patients (26%) in the standard radiation therapy arm and five

patients (10%) in the shorter course arm did not complete the treatment once it had started, and five other patients withdrew from the study before the treatment began. All patients eventually had their treatment discontinued due to clinical deterioration.

The RCT by Phillips et al (35) compared 35 Gy in 10 fractions to 60 Gy in 30 fractions in 68 patients who were over 45 years old (median age 59 years). The median survival was 10.3 months for patients in the 60 Gy arm and 8.7 months in the 35 Gy arm ( $p=0.37$ ). When the treatment arms were adjusted for histology, age, and performance status, the difference in median survival was still not significantly different.

### ***Brachytherapy***

Brachytherapy involves the placement of radioactive seeds interstitially in tumours. Because of the rapid decrease in dose outside the high-dose volume, there is relative sparing of adjacent normal tissues. As well, the low dose rate in brachytherapy (1 cGy/minute) compared with the dose rate in external radiotherapy (100-200 cGy/minute) is better tolerated by normal tissues, which allows a higher dose to be delivered. This increase in local dose might be beneficial in malignant glioma in view of the fact that 95% of these tumours are unifocal at presentation, and 90% of tumours recur within 2 cm of their original location.

There are two randomized trials of brachytherapy (36,37). Laperriere et al randomly assigned 140 patients to external radiotherapy delivering 50 Gy in 25 fractions over five weeks (69 patients) or external radiotherapy plus temporary stereotactic iodine-125 implants delivering a minimum peripheral tumour dose of 60 Gy (71 patients) (36). The Cox proportional hazards model revealed that the following factors were associated with improved survival: treatment at recurrence (chemotherapy or reoperation) (RR, 0.6;  $p=0.004$ ) and KPS greater than or equal to 90 (RR, 0.6;  $p=0.007$ ). Randomization to the implant arm was associated with a RR of 0.7 ( $p=0.07$ ). Median survival for patients randomized to brachytherapy versus no brachytherapy was 13.8 versus 13.2 months, respectively ( $p=0.49$ ). They concluded that stereotactic radiation implants had not demonstrated a statistically significant improvement in survival in the initial management of patients with malignant glioma.

The Brain Tumor Cooperative Group (BTCG) performed a randomized study of radiotherapy plus BCNU with and without interstitial radiation, using an implant that delivered a total dose of 60 Gy at the tumour periphery (37,38). The BTCG reported that the median survival for the patients receiving radiotherapy, BCNU and interstitial radiation (treatment group) was 68.1 weeks, and the median survival for the patients receiving radiotherapy and BCNU (control group) was 58.8 weeks. Despite the difference in median survival, overall survival was not significantly different between the groups ( $p=0.101$ ). The results of that RCT are consistent with those of Laperriere et al (36).

### ***Hyperthermia***

Hyperthermia refers to the exposure of body tissues to high temperatures. Hyperthermia has several effects that are complementary to brachytherapy. Combining these two therapeutic approaches may result in enhanced effect for the following reasons: heat is cytotoxic as a single modality, cells in S phase (more resistant to irradiation) are sensitive to heat, cells in a low-pH and hypoxic environment (resistant to irradiation) are more sensitive to heat, and heat inhibits the repair of sub-lethal damage from x-rays and has a more than additive effect when combined with x-rays (76).

Sneed et al reported a randomized study of hyperthermia in addition to brachytherapy as part of the initial management of patients with malignant astrocytoma (39). One hundred and twelve patients entered the study and completed external irradiation to a dose of 59.4 Gy with oral hydroxyurea. Because of tumour progression or patient refusal, only 79 patients were randomized to a brachytherapy boost (39 patients) alone or a brachytherapy boost with hyperthermia (40 patients). Only 69 of the 79 randomized patients received their allocated

treatment. Brachytherapy was delivered utilizing high-activity iodine-125 seeds stereotactically placed to deliver a total dose of 60 Gy to the periphery of the tumour at dose rates of 40-60 cGy/hour. Hyperthermia was delivered using microwave antennas, and a 30-minute hyperthermia session was delivered once prior to brachytherapy and once subsequent to removal of the iodine seeds. Median survival was 80 and 76 weeks for the hyperthermia and no-hyperthermia patients, respectively (logrank  $p=0.04$ ) in an intention-to-treat analysis of 79 patients. However, that four-week improvement in median survival was associated with increased toxicity, including neurological changes and seizures. There was a high rate of reoperation in that series, with 19/33 (58%) of brachytherapy boost-only patients undergoing 23 reoperations, and 25/36 (69%) of brachytherapy and hyperthermia patients undergoing 35 reoperations. Of note is the fact that 107 of 112 eligible patients had tumour progression at the time the study was reported.

### ***Particle Therapy***

Particle therapy refers to the use of sub-atomic particles as a form of treatment as opposed to photons. These particles include neutrons, protons, helium ions, and heavier nuclei, and negative pi mesons (pions). The use of these particle beams offers two possible advantages over the use of photons: better dose localization to the tumour volume and greater biologic effect. Fast neutrons are neutrons that are produced at higher energies (usually in a cyclotron) than the spectrum of energies associated with neutrons produced in a nuclear reactor; these latter neutrons are referred to as slow or thermal neutrons. Fast neutrons that have been studied have similar depth-dose characteristics to a cobalt unit, and, as such, do not offer any improved dose localization effect but have been studied predominantly for their possible biologic advantages over photons.

Five randomized trials have evaluated particle therapy (40-44) (Table 4). None of those trials detected a significant survival benefit for particle therapy. In the randomized, dose-searching study by the RTOG (41), autopsies were performed on 35 patients at all dose levels. There were some patients with both radiation damage to normal brain tissue and evidence of viable tumour. No evidence was found for a therapeutic window using this particular treatment regimen. Autopsies performed in the earlier RTOG study (40) revealed actively growing persistent tumour in all photon-treated patients compared to no evidence of actively growing tumour in the majority of neutron-treated patients. In the earlier study by Duncan et al (40), all patients who died had evidence of residual brain tumour. None had signs of radiation-related morbidity. The subsequent trial by Duncan et al (42) was discontinued prematurely as a result of neutron morbidity. In that study, four of nine patients treated by neutrons had evidence at autopsy of radiation-induced brain damage, and all had residual malignant glioma.

**Table 4. Randomized studies of particle therapy in malignant glioma.**

Study (Reference)	Treatment	# Patients Randomized (Analyzed)	Median Survival (Months)	p value
Griffin et al, 1983 (RTOG) (40)	50 Gy photon WBRT + 15Gy photon boost	83 (78)	8.6	n.s.
	50 Gy photon WBRT + 15Gy neutron boost	83 (80)	9.8	
Laramore et al, 1988 (RTOG) (41)	45 Gy photon WBRT + 3.6 Gy neutron boost	17 (17)	13.9	n.s.
	45 Gy photon WBRT + 4.2 Gy neutron boost	13 (12)	NR	
	45 Gy photon WBRT + 4.8 Gy neutron boost	29 (28)	NR	
	45 Gy photon WBRT + 5.2 Gy neutron boost	53 (44)	8.6	
	45 Gy photon WBRT + 5.6 Gy neutron boost	61 (59)	NR	
	45 Gy photon WBRT + 6.0 Gy neutron boost	30 (30)	NR	
Duncan et al, 1989 (42)	47.5 Gy photon	16 (16)	11	n.s.
	13.8 Gy neutron	18 (17)	7	
Duncan et al, 1986 (43)	47.5 Gy photon	30 (NR)	8	n.s.
	5.1 Gy neutron + 28.5 Gy photon	31 (NR)	4	
Pickles et al, 1997 (44)	60 Gy photon	NR (41)	10	n.s.
	33-34.5 Gy pion	NR (40)	10	

Note: NR indicates not reported; n.s., not statistically significant; WBRT, whole brain radiation therapy.

### **Sensitizer Studies**

Radiosensitizers are chemicals that increase the lethal effects of radiation. Many chemicals have been found to fit this definition; however, only those that have demonstrated a potential differential effect between tumour and normal tissues deserve further investigation. The two major classes of compounds investigated to date are hypoxic cell sensitizers and halogenated pyrimidines. Recently, the concurrent administration of radiotherapy with chemotherapy drugs, such as temozolomide, has been investigated for its radiosensitization effects.

#### *Hypoxic cell sensitizers*

In the boundary zones of necrotic areas in malignant glioma, there presumably exist tumour cells that are hypoxic but viable. Laboratory studies have established that hypoxic cells are significantly more resistant to radiation than oxic cells by an order of 2.5 to three. Hypoxic cell sensitizers would thus sensitize the hypoxic tumour cells without increasing the radiation effect on the already well-oxygenated normal tissues.

Urtasun et al initially reported a positive effect of metronidazole in a small randomized study in 1976 (45). However, the patient numbers were small, and the median survival of four months with radiation alone was considerably less than seen in most other studies. Since then, there have been 11 additional randomized studies (involving 1,605 patients) that have not shown any benefit from the addition of nitroimidazoles to various combinations of radiotherapy and chemotherapy (46-54) (Table 5).

There have been two meta-analyses examining the potential value of hypoxic cell sensitizers in the treatment of malignant gliomas (55,56). Overgaard pooled the same 13 randomized trials shown in Table 5 and reported a mortality OR of 1.04 (95% CI, 0.82 to 1.26; p=0.71) (55). Overgaard did not describe the search methods or the methods used to pool the data, and no quality assessment of the included studies was done. In contrast, Huncharek (56) conducted a comprehensive literature search from 1970 to 1996, provided selection criteria, described the statistical methods used to pool the data, and tested for heterogeneity. In addition, data were extracted by two independent reviewers. Huncharek pooled one-year survival data from nine randomized trials using misonidazole in the treatment of high-grade astrocytoma. Of note, two reports of the same study were included (15,74) as well as a preliminary report of the RTOG study by Nelson et al rather than the final report, which was published in 1986 (53). The results demonstrated no statistically significant difference in one-

year survival for misonidazole compared with the control (OR, 0.92; 95% CI, 0.77 to 1.09; p-value not stated) (56). There was no significant heterogeneity. Huncharek concluded that “misonidazole treatment is associated with an approximately 8% improved one-year survival compared with non-misonidazole treatment arms,” which does not follow from the nonsignificant results of the meta-analysis.

**Table 5. Randomized studies comparing sensitized radiotherapy with nitroimidazoles to radiotherapy alone in malignant glioma.**

Study (Reference)	Hypoxic Drug Studied	Total # Patients	Median Survival (Months) Sensitizer	Median Survival (Months) Radiation	p value
Urtasun, 1976 (45)	Metronidazole	29	7	4	p<0.02
Bleeheh, 1981 (46)	Misonidazole	38	9	7	n.s.
Urtasun, 1982 (47)	Metronidazole	36	5	6	n.s.
	Misonidazole	42	7	6	n.s.
Sack, 1982 (48)	Misonidazole	102	10	12	n.s.
EORTC, 1983 (49)	Misonidazole	163	11	12	n.s.
MRC, 1983 (50)	Misonidazole	384	8	9	n.s.
Stadler, 1984 (51)	Misonidazole	45	13.8	9.8	n.s.
Shin, 1985 (15)	Misonidazole	86	12	10	n.s.
Hatlevoll, 1985 (52)	Misonidazole	244	10	10	n.s.
Nelson, 1986 (53)	Misonidazole	146	11.5	12.5	n.s.
Okkan, 1988 (54)	Ornidazole	40	15	10	n.s.
Deutsch, 1989 (17)	Misonidazole	279	9	10	n.s.

Note: n.s., not statistically significant.

*Halogenated pyrimidines*

The halogenated pyrimidines 5–bromodeoxyuridine (BUdR) and 5–iododeoxyuridine (IUdR) are similar to the normal DNA precursor thymidine, having a halogen substituted in place of a methyl group. These compounds are incorporated into DNA in place of thymidine in a competitive fashion, which leads to an increased sensitivity of cells incorporating these compounds to the effects of radiation and ultraviolet light. The rationale for using these compounds in the treatment of brain tumours is that mitotically active tumour cells are much more likely to incorporate these compounds than the slowly replicating glial and vascular cells in the normal brain.

Phillips et al reported an increase in median survival for anaplastic astrocytoma patients from 82 weeks in prior studies to 252 weeks in patients treated with radiation, BUdR, and chemotherapy (77). There was no significant improvement seen with the use of BUdR for patients with glioblastoma. As a result of that observation, the RTOG embarked on a randomized study for patients with anaplastic astrocytoma: 60 Gy in 30 fractions with and without BUdR, both arms followed by PVC chemotherapy. The study was closed prematurely when the initial 189 patients were analysed. The one-year survival rate for radiotherapy, PVC, and BUdR was 68% versus 82% for radiotherapy plus PVC (one-sided p=0.96) (57).

*Temozolomide*

Recent clinical studies have explored the administration of radiotherapy concurrently with chemotherapy agents to enhance outcome. Several in vitro studies have demonstrated that temozolomide (TMZ), an oral alkylating agent, can have additive or synergistic effects when

used with x-rays to treat glioma cells (78,79). Stupp et al conducted a randomized phase 3 trial of 573 patients with glioblastoma comparing radiotherapy alone with radiotherapy plus TMZ (58). TMZ was administered with and after radiotherapy. The addition of TMZ to radiotherapy resulted in both clinically and statistically significant improvement in survival. The median survival was 14.6 months with radiotherapy plus TMZ and 12.1 months with radiotherapy alone, with a median follow-up of 28 months. The two-year survival rate was 26.5 percent with radiotherapy plus temozolomide and 10.4 percent with radiotherapy alone. A similar randomized trial of 130 patients with glioblastoma multiforme by Athanassiou et al also demonstrated a statistically significant benefit in median and overall 1-year survival for radiotherapy plus concurrent and adjuvant TMZ compared to radiotherapy alone (59). The results of those studies suggest a benefit of combined treatment with radiotherapy and TMZ in glioblastoma patients.

While results suggest a treatment benefit of concurrent radiotherapy with TMZ, those studies are unable to distinguish the benefit as a radiosensitization effect, an adjuvant effect, or a combination of both effects. Since neither study reported results for radiotherapy plus concurrent TMZ without the addition of adjuvant TMZ, any radiosensitization effect would be masked by the effects of adjuvant treatment. However, since most prior studies of chemotherapy in the adjuvant setting have been negative, it is possible that the novel concurrent administration of TMZ in those studies may be the reason for the demonstrated survival benefit. Ongoing and future trials may further clarify the effects of concurrent chemotherapy agents with radiotherapy.

### ***Radiosurgery***

Radiosurgery refers to the delivery of a single fraction of radiotherapy utilizing stereotactic techniques to conform the dose to the enhancing tumour. Several reports detailing the use of radiosurgery as a radiation dose boost after the completion of conventionally fractionated radiotherapy have appeared in the literature in the past few years (60-70).

Souhami et al (71) published a report of an RCT that randomized 203 patients with glioblastomas to either stereotactic radiosurgery with radiotherapy and BCNU or radiotherapy and BCNU alone. They measured quality of life and mental status in addition to survival and toxicity. They detected no significant differences between treatment arms in terms of median survival, patterns of failure, quality-of-life deterioration, and mental status. Compliance was a problem in the stereotactic radiosurgery arm, with 18% of patients having unacceptable deviations. Compliance was not a problem in the radiotherapy and BCNU arm.

### ***Radiation Toxicity***

Radiotherapy has long been recognized to cause possible significant deleterious effects on normal brain tissue. Common acute effects include alopecia, scalp erythema, serous otitis media, nausea, and fatigue. Late effects include radiation necrosis, dementia, and effects on higher cognitive functioning (80). Many of these clinical late effects can be related to white matter changes noted on MRI and CT (81,82). Corn et al found that the severity and frequency of white matter injury was statistically associated with increasing radiation dose in a phase I/II dose-seeking trial of hyperfractionated cranial radiotherapy (83).

In view of the high rate of recurrence at the original site in patients treated with malignant gliomas of the brain, many of the reviewed therapies in this systematic review deal with strategies to increase the radiation dose either directly or through mechanisms of radiation sensitization. Inherent in those strategies is a possible increased risk of radiation damage to nearby normal brain structures, which would be associated with toxicity or even shortened survival. Radiation toxicity can sometimes be very difficult to ascertain in patients with glioblastoma multiforme for two reasons: the short median survival of less than one year is probably not long enough for late radiation toxicity to be expressed in many of these patients,

and those tumours are associated with large zones of necrosis that may obscure radiation damage both on imaging studies and at autopsy.

Patients with anaplastic-atypical astrocytoma have a median survival of approximately three years and represent a group of patients who are related to the more aggressive neoplasms discussed in this systematic review and for whom the same types of experimental treatments have been attempted (84). Laramore et al compared three cohorts of patients treated on different RTOG protocols with photons alone, photons with chemotherapy, and photons with a neutron boost (84). The survival rates for those three cohorts were 3.0 years, 2.3 years, and 1.7 years, respectively. This suggests that more aggressive treatments were associated with a decrease in survival, and a warning that, in future studies, patients should be made aware of the possible increased risks of adverse events that may be associated with a decrease in survival over conventional therapy.

## **DISCUSSION**

### **Conventional Radiation**

Several randomized studies support the use of postoperative radiotherapy in the management of newly diagnosed adult patients with malignant glioma as the routine standard practice (Table 2). Two randomized studies demonstrated no significant difference in survival rates for whole brain radiation versus more local fields that encompass the enhancing primary plus a 2 cm margin (9,10). In view of the fact that greater than 90% of recurrences occur at the primary site, most centres and all ongoing multicentre studies in malignant glioma have now eliminated the use of whole brain radiation in favour of local radiation fields for the whole course of treatment, with no apparent difference in survival. Until we are better able to control the primary tumour, recurrence at a distance from the primary site remains an uncommon occurrence.

The Medical Research Council (UK) study demonstrated a small improvement in survival with 60 Gy in 30 fractions over 45 Gy in 20 fractions (11). The joint study of the RTOG/ECOG did not show any advantage of 70 Gy over 60 Gy (12). There are no randomized data examining 50 Gy or 54 Gy versus 60 Gy in that patient population. There was no advantage of a brachytherapy implant delivering an additional minimal tumour dose of 60 Gy in addition to 50 Gy in 25 fractions compared with 50 Gy in 25 fractions alone in the randomized Toronto brachytherapy study (36). Accordingly, the evidence would support the use of postoperative radiotherapy to a total dose in the range of 50 to 60 Gy utilizing conventional fractionation.

### **Radiation Dose Intensification**

Although investigators were able to safely escalate the dose to 72 Gy, utilizing hyperfractionation, randomized studies did not demonstrate any advantage over conventionally fractionated doses in the range of 50 to 60 Gy.

One randomized study of accelerated fractionation compared with conventional fractionation that has been performed demonstrated no survival difference (22). The survival data from the reported cohorts of patients were within the range of expected results with conventional fractionation. However, those shorter regimens were well tolerated and did not show any increased incidence of late sequelae. That information may prove useful in the future if any other alterations in treatment might be advantageously combined with an accelerated fractionation regimen.

The main aim of hypofractionation is to achieve equivalent survival with a shorter radiation scheme. The concern with utilizing hypofractionation to higher total doses (in the range of 45 to 50 Gy) is a possible increased risk of late radiation morbidity. The subset of patients for whom a shorter fractionation scheme would be indicated are those who benefit less from postoperative radiotherapy, namely patients with adverse prognostic factors (older age and/or a poor performance status). The doses utilized for those patients ranged from 30 Gy in six

fractions to 42 Gy in 14 fractions (27-30,32). That option would be particularly appropriate for patients who are both older and with a poor performance status, as there remains some doubt about the use of these shorter radiation approaches in older patients with a good performance status (28). Alternatively, in patients who are bedridden and confused despite surgery and dexamethasone, it would be reasonable to consider supportive care only.

The sole randomized study on hypofractionation examined a three-week course of irradiation spread out over 11 weeks compared with a five-week course of treatment (33). While there was no significant survival difference overall, the author reported a survival advantage at two years favouring the hypofractionated arm for the subset of 44 patients with glioblastoma. This is an interesting observation that would require further study, but differentiating anaplastic astrocytoma from glioblastoma is well known to be difficult (85). Based on those data, the DSG members remained unconvinced that a hypofractionated course of irradiation confers a true survival advantage for patients with malignant glioma.

Existing data do not support brachytherapy as part of the initial management of patients with malignant glioma. Although a single randomized trial found that brachytherapy given with hyperthermia resulted in a four-week improvement in median survival over brachytherapy alone, the modest gain may not justify the added cost and morbidity associated with that approach.

Studies did not demonstrate any benefit for the use of particle therapy over conventional photon radiotherapy for patients with malignant glioma. Those modalities remain as investigational approaches.

### **Sensitized Radiation**

Randomized trials of nitroimidazoles and halogenated pyrimidines have not demonstrated any survival advantage. There are several possible reasons for the lack of a positive effect in those studies. The intratumoural concentrations of nitroimidazoles may not have been adequate as a result of dose-limiting neurotoxicity. It is possible that reoxygenation occurs during the five to six weeks of daily fractionated radiotherapy to counter the effect of hypoxia. Alternatively, hypoxia may not be a rate-limiting phenomenon in this disease.

Results of two randomized trials (58,59) suggest a possible radiosensitization effect of TMZ when administered concurrently with radiotherapy. A survival benefit was observed in patients with glioblastoma who received radiotherapy plus concurrent and adjuvant TMZ compared to patients who received radiotherapy alone. Further RCTs will clarify the effect of administering radiotherapy with chemotherapy to enhance treatment effect.

### **Radiosurgery**

A new RCT comparing stereotactic radiosurgery with radiotherapy and BCNU to radiotherapy and BCNU alone was recently published (71). The results of the RCT indicate that stereotactic radiosurgery offers no survival benefit to patients with glioblastomas. The Neuro-oncology DSG will wait for further evidence regarding stereotactic radiosurgery before making recommendations regarding its use.

### **ONGOING TRIALS**

The Physician Data Query (PDQ) database ([http://www.cancer.gov/search/clinical\\_trials/](http://www.cancer.gov/search/clinical_trials/)) was searched for reports of ongoing clinical trials and the following trial was located:

**EORTC-22972, EORTC-26991, and MRC-BR10.** Phase III randomized study of adjuvant conventional radiotherapy with or without stereotactic boost radiotherapy in patients with high-grade glioma. A total of 605 patients were to be accrued for this study. This study is now closed; no published results were identified in the literature yet. The study is available at:

[http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=67096&version=HealthProfessional&protocolsearchid=982279#PublishedResults\\_CDR0000067096](http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=67096&version=HealthProfessional&protocolsearchid=982279#PublishedResults_CDR0000067096).

## **JOURNAL REFERENCE**

The Neuro-oncology DSG published the following systematic review in 2002 based on the evidence described in this practice guideline: Laperriere N, Zuraw L, Cairncross G. Radiotherapy for newly diagnosed malignant glioma in adults: a systematic review. *Radiother Oncol.* 2002; 64:259-73.

## **ACKNOWLEDGEMENTS**

The Neuro-oncology Disease Site Group would like to thank Dr. Normand Laperriere, Dr. James Perry, Dr. Gregory Cairncross, Ms. Lisa Zuraw, Ms. Alexandra Chambers and Ms. Karen Spithoff for taking the lead in drafting, revising, and updating this evidence-based series report.

For a complete list of the Neuro-oncology Disease Site Group members and the Practice Guidelines Coordinating Committee group members, please visit the CCO web site at <http://www.cancercare.on.ca>.

### *Funding*

The Program in Evidence-based care is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

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### **Evidence-based Series #9-3: Section 3**

## **Radiotherapy for Newly Diagnosed Malignant Glioma in Adults: Guideline Development and External Review - Methods and Results**

*N. Laperriere, J. Perry, L. Zuraw, and members of the Neuro-oncology Disease Site Group*

A Quality Initiative of the  
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)  
Developed by the Neuro-oncology Disease Site Group

**Original Report Date: September 19, 2000**

**Current Report Date: November 2, 2005**

### **THE PROGRAM IN EVIDENCE-BASED CARE**

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

### **The Evidence-based Series: A New Look to the PEBC Practice Guidelines**

Each Evidence-based Series is comprised of three sections.

- *Section 1: Clinical Practice Guideline.* This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
- *Section 2: Systematic Review.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- *Section 3: Guideline Development and External Review: Methods and Results.* This section summarizes the guideline development process and the results of the formal external review

by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

## **DEVELOPMENT OF THIS EVIDENCE-BASED SERIES**

### **Development and Internal Review**

This evidence-based series was developed by the Neuro-oncology Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care (PEBC). The series is a convenient and up-to-date source of the best available evidence on radiotherapy for newly diagnosed malignant glioma, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

The Neuro-oncology DSG reviewed the available evidence and developed recommendations to address the following clinical questions:

1. What is the role of radiotherapy in adult patients with newly diagnosed malignant glioma?
2. If radiotherapy is offered, what are the optimal radiotherapy characteristics?

The practice guideline with recommendations is presented in Section 1. This practice guideline report has been reviewed and discussed by the Neuro-oncology DSG on several occasions and it was approved with the addition of the following general comments.

Many of the studies discussed in the systematic review were performed over the last two to three decades. There have been major technological advances in both the delivery of radiotherapy and in diagnostic imaging in the last five to ten years, such that results and recommendations based on those older data may no longer be pertinent. Until new evidence emerges revisiting many of the issues raised in this evidence-based series, the DSG agreed that the current recommendations apply. However, the most recent literature search update provided sufficient evidence to recommend the addition of concurrent TMZ to conventional radiotherapy regimens.

Additionally, most of those older studies did not address toxicity or quality of life. This is particularly pertinent for studies where higher intensities of therapy were being investigated. It is very possible that higher intensity therapies may prolong life but at a significant cost in terms of quality of life, such that patients and physicians should have that information available to be able to make informed choices among the therapeutic options. It is strongly recommended that future studies in patients with brain tumours include measures of toxicity and quality of life.

Postoperative radiotherapy as an appropriate recommendation for patients is well supported by randomized studies and remains standard therapy. With regard to the dose issue, only the Medical Research Council (UK) study of 60 Gy in 30 fractions compared with 45 Gy in 20 fractions showed a small statistically significant benefit for the higher dose (12). No other randomized studies of dose escalation have shown any benefit compared with conventional doses in the range of 50 to 60 Gy. For that reason, the DSG felt that doses of 60 Gy with conventional fraction sizes were acceptable, particularly in view of the fact that higher doses are likely associated with higher toxicity and increased costs and inconvenience for the patient, in a disease that remains incurable.

The hypofractionated dose utilized in the study by Glinski (33), given over three months, is an extremely unusual fractionation, and one that the DSG does not recommend.

All other studies of hyperfractionation, radiation sensitizers, or particle therapy have thus far failed to demonstrate a benefit, and those approaches remain within the domain of experimental therapy. In view of the poor results of conventional radiotherapy in this disease, the DSG recommends that patients be encouraged to participate in properly conducted experimental studies.

**External Review by Ontario Clinicians**

Following the review and discussion of Sections 1 and 2 of this evidence-based series, the Neuro-oncology DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

**BOX 1:  
DRAFT RECOMMENDATIONS** (approved for external review June 14, 2000)

<p><i>Target Population</i></p> <p>These draft recommendations apply to newly diagnosed adults with histologic confirmation of the following diagnoses: glioblastoma multiforme, malignant astrocytoma, malignant astrocytoma grade 3, malignant astrocytoma grade 4, malignant glioma, or gliosarcoma.</p>
<p><i>Recommendations</i></p> <ul style="list-style-type: none"> <li>• Postoperative external beam radiotherapy is recommended as standard therapy.</li> <li>• The high-dose volume should incorporate the enhancing tumour plus a limited margin (e.g. 2 cm) for the planning target volume, and the total dose delivered should be in the range of 50-60 Gy in fraction sizes of 1.8-2.0 Gy.</li> <li>• Radiation dose intensification and radiation sensitizer approaches are not recommended as standard care.</li> </ul>
<p><i>Qualifying Statements</i></p> <ul style="list-style-type: none"> <li>• Conventional radiotherapy as discussed above is considered standard treatment for patients older than age 70. There are preliminary data to suggest the same survival benefit can be achieved with less morbidity using a shorter course of radiotherapy. This is now being tested in Canada in a randomized study, and patients are encouraged to participate.</li> <li>• Since the outcome is so poor following conventional radiotherapy for patients older than age 70 with a poor performance status, supportive care only is a reasonable therapeutic option in these patients.</li> </ul>

**Methods**

Practitioner feedback was obtained through a mailed survey of 65 practitioners in Ontario (13 medical oncologists, 15 radiation oncologists, 22 surgeons, 13 neurologists, one hematologist, and one pathologist). The survey consisted of 21 items evaluating the methods, results, and interpretive summary used to inform the draft recommendations outlined and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Neuro-oncology Disease Site Group reviewed the results of the survey.

**Results**

Key results of the practitioner feedback survey are summarized in Table 6. The return rate was 59%, and 29 practitioners completed the questionnaire. Twenty-five practitioners (86%) agreed that the document should be approved as a practice guideline, and 86% agreed that they would use it in their own clinical practice.

**Table 6. Responses to eight items on the practitioner feedback survey.**

Item	Number (%)*		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a clinical practice guideline, as stated in the “ <i>Choice of Topic</i> ” section of the report, is clear.	28 (96%)	0	0
There is a need for a clinical practice guideline on this topic.	27 (93%)	1 (3%)	0
The literature search is relevant and complete.	26 (90%)	2 (7%)	0
The results of the trials described in the report are interpreted according to my understanding of the data.	26 (90%)	1 (3%)	1 (3%)
The draft recommendations in this report are clear.	25 (86%)	1 (3%)	2 (7%)
I agree with the draft recommendations as stated.	25 (86%)	2 (7%)	1 (3%)
This report should be approved as a practice guideline.	25 (86%)	2 (7%)	2 (7%)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	<b>Very likely or likely</b>	<b>Unsure</b>	<b>Not at all likely or unlikely</b>
	25 (86%)	2 (7%)	1 (3%)

\* Percentages may not total 100% due to missing data.

**Summary of Written Comments**

Nine (31%) respondents provided written comments. The major substantive comment concerned the qualifying statements, which several practitioners misinterpreted. Feedback indicated that the age group to which the qualifying statements apply (older versus younger than 70 years) was not clear. There were requests for more information on stereotactic radiosurgery, surgery alone versus radiation therapy, extent of surgery (biopsy with or without gross total resection), and data on “time lost from survival” caused by having to go to the hospital for treatment and recovering from radiation-induced complications. One practitioner indicated a need for trials to assess new drugs with external beam radiotherapy.

**Modifications/Actions**

Practitioner feedback did not indicate a need to modify the draft recommendation, although the first qualifying statement was reworded to make it clear that it applies to patients older than 70 years. Surgery for malignant glioma will be addressed in a separate guideline report, which is being prepared by the Neuro-oncology DSG.

**Practice Guidelines Coordinating Committee Approval Process**

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Neuro-oncology DSG and the Practice Guidelines Coordinating Committee.

Box 2 summarizes the clinical recommendations and supporting evidence developed by the panel. Recommendations were updated in November 2005 to include the most recent evidence obtained through literature search updates.

**BOX 2:**  
**PRACTICE GUIDELINE RECOMMENDATIONS** (November 2, 2005)

*Target Population*

These draft recommendations apply to newly diagnosed adults with histologic confirmation of the following diagnoses: glioblastoma multiforme, malignant astrocytoma, malignant astrocytoma grade 3, malignant astrocytoma grade 4, malignant glioma, or gliosarcoma.

*Recommendations*

- Postoperative external beam radiotherapy is recommended as standard therapy.
- The high-dose volume should incorporate the enhancing tumour plus a limited margin (e.g. 2 cm) for the planning target volume, and the total dose delivered should be 60 Gy in 2.0 Gy fractions, with concurrent temozolomide at 75 mg/m<sup>2</sup>.
- Radiation-dose intensification and radiation sensitizer approaches are not recommended as standard care.

*Qualifying Statements*

- A randomized study has established the equivalence of 60 Gy in 30 fractions to 40 Gy in 15 fractions in older patients (>60 years)
- Since the outcome following conventional radiotherapy is so poor in older patients with a poor performance status, supportive care alone is a reasonable therapeutic option in these patients.

*Funding*

The Program in Evidence-based care is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

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