Radiotherapy for newly diagnosed malignant glioma in adults: a systematic review

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Abstract

**Purpose:** A systematic review was conducted to develop guidelines for radiotherapy in adult patients with newly diagnosed malignant glioma.

**Methods:** MEDLINE, CANCERLIT, the Cochrane Library, and relevant conference proceedings were searched to identify randomized trials and meta-analyses.

**Results:** Pooling of six randomized trials detected a significant survival benefit favouring post-operative radiotherapy compared with no radiotherapy (risk ratio, 0.81; 95% confidence interval, 0.74 to 0.88, \( P < 0.00001 \)). Two randomized trials 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. A randomized trial detected a small improvement in survival with 60 Gy in 30 fractions over 45 Gy in 20 fractions. Radiation dose intensification and radiation sensitizer approaches have not demonstrated superior survival rates compared with conventionally fractionated doses of 50–60 Gy.

**Conclusions:** Post-operative external beam radiotherapy is recommended as standard therapy for patients with malignant glioma. 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. Radiation dose intensification and radiation sensitizer approaches are not recommended as standard care. For patients older than age 70, preliminary data suggest that the same survival benefit can be achieved with less morbidity using a shorter course of radiotherapy. Supportive care alone is a reasonable therapeutic option in patients older than age 70 with a poor performance status. Copyright © 2002 Cancer Care Ontario. Published by Elsevier Science Ireland Ltd. All rights reserved.

**Keywords:** Malignant glioma; Radiotherapy; Practice guideline; Systematic review

1. Introduction

Malignant gliomas are the most common primary brain tumour in adults, occurring at a rate of five cases per 100 000 population per year. Subsequent to the performance of optimal surgical resection or biopsy, radiotherapy is the dominant form of therapy administered post-operatively. Unlike the case in 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 radiation dose in an effort to improve local control rates and survival in a disease which in most cases is invariably fatal.

Between, 1982 and 1994, there were 3279 cases of glioblastoma recorded in the Ontario Cancer Registry [53]. This 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

1 Mark Bernstein MD, George Browman MD, Philip Davey MD, Stanley Gertler MD, Donald Lee MD, Chris Leighton MD, Samuel Ludwin MD, David Macdonald MD, Arlan Mintz MD, James Perry MD, Nancy Read MD, Helen Rhhyderch RN, Anthony Whitton MD, and two community representatives also contributed to the development of this practice guideline. Please see the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) web site (http://www.cancercare.on.ca/ccopgi/) for a complete list of current Neuro-Oncology Disease Site Group members.
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.

The Neuro-Oncology DSG reviewed the 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?

In this systematic review, the term ‘malignant glioma’ encompasses all of the following diagnoses: glioblastoma multiforme, malignant astrocytoma, malignant astrocytoma grade 3, malignant astrocytoma grade 4, malignant glioma, or gliosarcoma. This review is not intended to encompass the entities malignant mixed oligoastrocytoma or anaplastic oligodendroglioma. There is now an emerging literature specifically assessing the management of these entities separately from malignant gliomas in general. It is not possible to know what proportion of patients in prior studies harboured oligodendroglial neoplasms by today’s pathology criteria. We believe that in view of the relative rarity of these entities and the fact that most studies considered are randomized studies, that it is unlikely that the small proportion of patients with these uncommon neoplasms would change the conclusions arrived at in this review. This review is limited to radiation therapy issues.

2. Methods

2.1. Literature search strategy

MEDLINE (1966 to November 2000), CANCERLIT (1983 to November 2000) and the Cochrane Library (Issue 4, 2000) 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 1998–2000 meetings of the American Society of Clinical Oncology (ASCO) and the 1998–1999 meetings of American Society for Therapeutic Radiology and Oncology (ASTRO) was also conducted. The Physician Data Query (PDQ) database (http://cnetdb.nci.nih.gov/trialsrch.shtml) was searched for reports of on-going clinical trials. Relevant articles and abstracts were reviewed and the reference lists from these sources were searched for additional trials.

2.2. Inclusion criteria

Fully published articles and abstracts were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. Meta-analyses and randomized trials comparing various aspects of radiotherapy in patients with malignant glioma. Where no randomized trials were available, non-randomized studies were reviewed.
2. The outcome of interest was survival.

2.3. Synthesizing the evidence

One-year mortality data from the trials of post-operative radiotherapy versus no post-operative radiotherapy, and the trials of hyperfractionated radiotherapy versus conventional fractionation radiotherapy, were pooled in separate meta-analyses using the software package Metaanalyst3.998 (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 [14]. The pooled results were examined for statistically significant heterogeneity (P < 0.10). Results were expressed as risk ratios (RR), where a RR less than 1.0 favours the experimental group and a RR greater than 1.0 favours the control group.

3. Results

3.1. Literature search results

The literature search identified 40 randomized trials. All studies reviewed (randomized trials and other studies) are listed in Table 1. Six randomized trials compared conventional radiation with no radiation. In addition, four randomized trials examined the issue of radiation volume and radiation dose. Six 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, one randomized trial of hypofractionation, two randomized trials of brachytherapy, one randomized trial of hyperthermia, and five randomized trials of particle therapy were also reviewed. Thirteen randomized trials and two published meta-analyses of sensitized radiation were found. There were no randomized trials of radiosurgery compared with conventional radiotherapy alone.

Of the 40 randomized studies included in this systematic
review, data on the proportion of major prognostic factors between the randomized arms were available in 27 studies. There were no significant differences in the distribution of differing grades of malignant glioma or age in all 27 studies. One study [62] had a significant imbalance in the distribution of performance status between the randomized arms, and this issue is discussed in that specific study in the following section.

3.2. Conventional radiation versus no radiation

Table 2 presents the results from six randomized trials where one of the arms contained no post-operative radiotherapy and one of the arms contained post-operative conventionally fractionated external beam radiotherapy with or without chemotherapy [1,36,60,62,78,79]. Patients in one trial were randomized according to birth date [1]. In the other trials, the randomization procedure was acceptable [78,79] or not described [36,60,62]. Three patients withdrew from the trial by Shapiro et al. [62], and 11 patients in the trial by Andersen [1] 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 [60,78,79], two of which included results for both the total randomized population and the ‘valid study group’ (i.e. excluding the protocol violations) [60,79]. Kristiansen et al. [36] 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. [60] was PVC (procarbazine, vincristine, lomustine).

Five of the six trials demonstrated a statistically significant survival benefit for post-operative 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 [62]. In this study, the mean Karnofsky performance status (KPS) for the no-radiation arm was 71 versus 57% for the radiotherapy arm \((P, 0.05)\). This imbalance in a major prog-

<table>
<thead>
<tr>
<th>Study [Ref.]</th>
<th>Study group</th>
<th>Radiation dose Gy/ no. of fractions</th>
<th>No. of patients randomized (analyzed)</th>
<th>Median survival (weeks)</th>
<th>Overall survival (P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shapiro et al., 1976 [62]</td>
<td>CT</td>
<td>60</td>
<td>16 (16)</td>
<td>30</td>
<td>NR</td>
</tr>
<tr>
<td>Andersen, 1978 [1]</td>
<td>RT + CT</td>
<td>45/25</td>
<td>51 (51)</td>
<td>15&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Survival at 6 months</td>
</tr>
<tr>
<td>Walker et al., 1978 [78]&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Surgery alone</td>
<td>45/25</td>
<td>51 (51)</td>
<td>23&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Walker et al., 1980 [79]&lt;sup&gt;d&lt;/sup&gt;</td>
<td>CT</td>
<td>40–60/25–35</td>
<td>93 (68)</td>
<td>36&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Kristiansen et al., 1981 [36]&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Surgery alone</td>
<td>60/30–35</td>
<td>118 (118)</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Sandberg-Wollheim et al., 1991 [60]</td>
<td>CT</td>
<td>45/25</td>
<td>87 (87)</td>
<td>42</td>
<td>0.028</td>
</tr>
</tbody>
</table>

<sup>a</sup> CT, chemotherapy; NR, not reported; RT, radiotherapy.

<sup>b</sup> Calculated from survival curve.

<sup>d</sup> Multi-arm study that included a radiation alone arm and a radiation plus chemotherapy arm. For both studies by Walker et al. [78,79], only data from the radiation alone arm are shown in Table 2. Kristiansen et al. [36] 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).

<sup>c</sup> Only results for the evaluable patients were reported (31 patients in the surgery alone arm and 68 patients in the RT arm).
nostic factor and the small number of patients could explain the lack of a statistically significant survival benefit from post-operative radiotherapy in this 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. [79] demonstrated a significant survival benefit for post-operative radiotherapy. Only a non-significant trend towards improved survival was found when Sandberg-Wollheim et al. [60] analyzed the 139 patients in the ‘valid study group’ (median, 66 months for post-operative 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.

Fig. 1 illustrates the results of pooling the six randomized trials of post-operative radiotherapy versus no post-operative radiotherapy. There was a statistically significant survival benefit favouring post-operative radiotherapy compared with no radiation (RR, 0.81; 95% confidence interval (CI), 0.74–0.88, \( P < 0.00001 \)). There was no significant heterogeneity (\( \chi^2 = 6.73, P > 0.10 \)).

### 3.3. Radiation volume

Before the computed tomography (CT) and magnetic resonance imaging (MRI) 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 CT and MRI, the many reports documenting

<table>
<thead>
<tr>
<th>Study</th>
<th>Post-operative Radiotherapy</th>
<th>No Post-operative Radiotherapy</th>
<th>Risk Ratio for 1-year Mortality</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths</td>
<td>Total</td>
<td>Deaths</td>
<td>Total</td>
</tr>
<tr>
<td>Shapiro, 1976 (62)</td>
<td>12</td>
<td>17</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Andersen, 1978 (1)</td>
<td>44</td>
<td>51</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>Walker, 1978* (78)</td>
<td>52</td>
<td>68</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Walker, 1980 (79)</td>
<td>74</td>
<td>118</td>
<td>82</td>
<td>111</td>
</tr>
<tr>
<td>Kristiansen, 1981 (36)</td>
<td>51</td>
<td>80</td>
<td>35</td>
<td>38</td>
</tr>
<tr>
<td>Sandberg-Wollheim, 1991 (60)</td>
<td>34</td>
<td>84</td>
<td>50</td>
<td>87</td>
</tr>
<tr>
<td>TOTAL</td>
<td>267</td>
<td>418</td>
<td>264</td>
<td>340</td>
</tr>
</tbody>
</table>

*Only results for the evaluable patients were reported.

![Fig. 1. Pooled results of trials of post-operative radiotherapy (RT) versus no radiotherapy.](image)

\[
\text{Favours Post-operative RT } = \text{ Favours No Post-operative RT} \\
\text{overall risk ratio} = 0.81 \ (95\% \text{ CI, 0.74 to 0.88}}; \ p<0.00001
\]
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 asso-
ciated with whole brain irradiation [27,80]. Initially, lateral
opposed parallel pairs were utilized to deliver the regional
radiotherapy, but increasingly with the advent of confor-
mal 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 [63]. 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-radia-

tion enhancing tumour volume plus a 2 cm margin with the dose
prescribed to the 90% isodose contour. There were no statisti-
cally 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 9 fractions for a total of 58 Gy in 29 fractions and 26
patients to received 56 Gy in 28 fractions via local fields
[33]. The survival rates for the whole brain group versus the
local field boost group were 43 versus 39% at 2 years and 17
versus 27% at 4 years, respectively (P values not reported).
The differences in survival rates between the treatment
groups were not statistically significant. The small numbers
in this latter trial would suggest that one should be cautious
in interpreting the results.

### 3.4. Radiation dose with 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 [4]. 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%. This difference was statisti-
cally 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 esti-
mated 3-month improvement in median survival for 60 Gy
(P = 0.007).

Nelson et al. [48] reported on a joint study of the Radia-
tion 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) and originally reported by Chang
et al. in 1983 [8]. There were no statistically significant
differences in survival among any of the four arms. The
median survival times for the 60 and 70 Gy arms were 9.3
and 8.2 months, respectively.

### 3.5. Hyperfractionated radiotherapy

Hyperfractionation involves the use of a larger number of
smaller sized fractions to a total dose which 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 adminis-
tered. These cells divide very slowly, and are better able
to repair sub-lethal damage than neoplastic cells. Conse-
quently, there might be an advantage to administering multi-
ple 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 asso-
ciated 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 dependant on oxygen, which might be advantageous
given the known areas of hypoxia in these tumours.

Table 3 shows the results of six randomized studies of
hyperfractionated radiotherapy compared with convention-
ally fractionated radiotherapy [15,43,54,64,66,67]. All the
studies demonstrated no benefit on the experimental arm
except one study by Shin et al. where a survival advantage
was found for the hyperfractionated arm [67]. This 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 signifi-
cant imbalance in age distribution between the randomized
arms favouring the hyperfractionated arm [66]. The largest
study on hyperfractionation, reported by Scott et al., clearly
showed no benefit for the use of hyperfractionated radio-
therapy in malignant gliomas [64]. The experimental arm of
72 Gy in 60 fractions arose as the best arm from a rando-
mized 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 [47].

Stuschke and Thames [72] pooled data from three rando-
mized trials of hyperfractionation compared with conven-
tional radiotherapy [15,20,66]. The pooled results detected a
significant survival benefit favouring hyperfractionation
(odds ratio (OR), 0.67; 95% CI, 0.48–0.93; P = 0.02). To
identify the three trials included in this meta-analysis,
Table 3
Randomized studies of hyperfractionated radiotherapy compared with conventionally fractionated radiotherapy in malignant glioma

<table>
<thead>
<tr>
<th>Study [Ref.]</th>
<th>Hyperfractionated radiotherapy</th>
<th>Conventional radiotherapy</th>
<th>Overall Survival</th>
<th>Median survival (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fractionation time no. of patients randomized (analyzed)</td>
<td>Median survival (weeks)</td>
<td>Fractionation time no. of patients randomized (analyzed)</td>
<td></td>
</tr>
<tr>
<td>Payne et al., 1982 [54]</td>
<td>36–40 Gy/36–40 2 weeks n = NR (78)b</td>
<td>48c</td>
<td>50 Gy/25 5 weeks n = NR (79)b</td>
<td>48c NR Not significant</td>
</tr>
<tr>
<td>Shin et al., 1983 [66]</td>
<td>50 Gy/50 4 weeks n = 35 (35)</td>
<td>56</td>
<td>50 Gy/25 5 weeks n = 34 (34)</td>
<td>39 NR Not significant</td>
</tr>
<tr>
<td>Shin et al., 1985d [67]</td>
<td>6141 cGy/69 4.5 weeks n = 43 (43)</td>
<td>39</td>
<td>5800 cGy/30 6 weeks n = 38 (38)</td>
<td>27 0.007</td>
</tr>
<tr>
<td>Ludgate et al., 1988 [43]</td>
<td>4760 cGy/60 + 1000 cGy/5 5 weeks n = 42 (42)</td>
<td>46</td>
<td>4000 cGy/20 + 1000 cGy/5 5 weeks n = 34 (34)</td>
<td>32 NR Not significant</td>
</tr>
<tr>
<td>Deutsch et al., 1989d [15]</td>
<td>6600 cGy/60 6 weeks n = 154 (154)</td>
<td>45c</td>
<td>6000 cGy/30–35 6–7 weeks n = 152 (152)</td>
<td>43c NR Not significant</td>
</tr>
<tr>
<td>Scott et al., 1998d [64]</td>
<td>n = 520 evaluable glioblastoma 7200 cGy/60 6 weeks NR</td>
<td>44</td>
<td>6000 cGy/30 6 weeks NR</td>
<td>49 0.44</td>
</tr>
<tr>
<td></td>
<td>n = 107 evaluable anaplastic astrocytoma 7200 cGy/60 6 weeks NR</td>
<td>189</td>
<td>6000 cGy/30 6 weeks NR</td>
<td>215 0.81</td>
</tr>
</tbody>
</table>

NR, not reported.

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

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

d Both arms of these studies received BCNU.

e 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.

f 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.
MEDLINE and CANCERLIT were searched from 1980 to 1995. The search missed the trial by Ludgate et al. [43] and an updated report by Shin et al. in 1985 [67] on the trial by Fulton et al. [20]. Stuschke and Thames [72] reported their selection criteria and they noted that the trial by Payne et al. [54] 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. [20] were identified when study quality was assessed by Stuschke and Thames [72]. Specifically, nine of 42 patients in the hyperfractionated radiotherapy arm of the three-arm trial by Fulton et al. [20] 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 [43,66] as well as the trials by Shin et al. [67] and Deutsch et al. [15]. The results demonstrated no statistically significant survival benefit for hyperfractionated radiotherapy compared with conventional radiotherapy (RR, 0.89; 95% CI, 0.73–1.09; P = 0.27) (Fig. 2). There was no statistically significant heterogeneity ($\chi^2 = 6.27, P = 0.10$). The pooled results are consistent with the lack of benefit seen on the largest study on hyperfractionation reported by Scott et al. in abstract form [64]. This 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. This 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. [43] could not be included either because the survival curves were shown for three different age groups rather than for the total study group.

### 3.6. 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 2 or 3 fractions per day with normal sized fractions.

<table>
<thead>
<tr>
<th>Study</th>
<th>Hyperfractionated Radiotherapy</th>
<th>Conventional Radiotherapy</th>
<th>Risk Ratio for 1-year Mortality</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths</td>
<td>Total</td>
<td>Deaths</td>
<td>Total</td>
</tr>
<tr>
<td>Payne, 1982</td>
<td>48</td>
<td>78</td>
<td>44</td>
<td>79</td>
</tr>
<tr>
<td>Shin, 1983</td>
<td>16</td>
<td>35</td>
<td>23</td>
<td>34</td>
</tr>
<tr>
<td>Shin, 1985</td>
<td>25</td>
<td>43</td>
<td>30</td>
<td>38</td>
</tr>
<tr>
<td>Deutsch, 1989</td>
<td>86</td>
<td>154</td>
<td>87</td>
<td>152</td>
</tr>
<tr>
<td>TOTAL</td>
<td>175</td>
<td>310</td>
<td>184</td>
<td>303</td>
</tr>
</tbody>
</table>

![Fig. 2. Pooled results of trials of hyperfractionated radiotherapy (RT) versus conventional fractionation radiotherapy.](image)

Favours Hyperfractionated RT ≈ Favours Conventional RT

overall risk ratio = 0.89 (95% CI, 0.73 to 1.09; p=0.27)
Accelerated fractionation has been evaluated in a randomized study conducted by the European Organization for Research on Treatment of Cancer (EORTC) [29]. In protocol 22803, 340 patients were randomly assigned to conventional radiotherapy or accelerated fractionation with or without misonidazole. Accelerated fractionation consisted of 3 fractions of 2 Gy per day with a 4-h gap between fractions to deliver 30 Gy in 1 week. This treatment course was repeated after a 2-week break for a total of 60 Gy in 30 fractions in 4 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 [81]. 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 [5]. 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 6 weeks.

Two other small studies also found no improvement in survival or increased toxicity with accelerated fractionation schemes in malignant glioma [32,69]. One study evaluated 40 Gy in 20 fractions in 1 week as part of a randomized phase II study [24], while the other evaluated 60 Gy in 16 days using a single-arm phase II design [25].

### 3.7. 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 these patients.

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) [2,19,28,70,74]. The number of patients involved in these studies ranged from 25 to 38 years. The age criteria varied between ≥ 65 and 70 years and the Karnofsky Performance Status was generally ≤ 50. The following radiation schemes were used: 30 Gy in 6 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 these results were equivalent to what would have been expected with conventional radiotherapy for the distribution of prognostic factors in these patients, but Bauman et al. cautioned that elderly patients with a higher pretreatment KPS (>50) may benefit from a higher dose radiotherapy regimen [2].

Kleinberg et al. reported a study of 219 patients treated with 51 Gy in 17 fractions in 5.5 weeks [34]. The radiation treatment was 30 Gy in 10 fractions given to a large or whole brain field, and this was followed after a 2-week break by 21 Gy in 7 fractions to a reduced field. Patients were retrospectively assigned to six prognostic groups previously identified in a recursive partitioning analysis of the RTOG [12]. The six RTOG prognostic groupings were significantly predictive of outcome for patients treated with this shortened regimen (log rank P < 0.001). The median survival times for the patients by RTOG groups 1–6 were 68, 57, 22, 13, 8, and 5 months, respectively. Two-year survival rates were 64, 67, 45, 8, 3, and 3%, respectively. The median and 2-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. [34] 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 1-month intervals [22]. The first two courses of hypofractionated radiation were 20 Gy in 5 fractions to the whole brain, while the third course was a 10 Gy boost to the local tumour in 5 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 2 years; P < 0.05).

### 3.8. 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/min) compared with the dose rate in external radiotherapy (100–200 cGy/min) 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 [23,37]. Laprierre et al. [37] randomly assigned 140
implants had not demonstrated a statistically significant hyperthermia and no hyperthermia patients, respectively. Median survival was 80 and 76 weeks for the 30-min hyperthermia session was delivered once prior to the periphery of the tumour at dose rates of 40 cGy/h. A published report of the results is awaited.

3.9. 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 sublethal damage from X-rays and has a more than additive effect when combined with X-rays [70].

Sneed et al. reported a randomized study of hyperthermia in addition to brachytherapy as part of the initial management of patients with malignant astrocytoma [71]. 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/h. Hyperthermia was delivered using microwave antennas, and a 30-min 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 (log rank $P = 0.04$) in an intention-to-treat analysis of 79 patients. However, this 4-week improvement in median survival was associated with increased toxicity, including neurological changes and seizures. There was a high rate of reoperation in this 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 of reporting the study.

3.10. Particle therapy

Particle therapy refers to the use of subatomic 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 [16,17,24,38,56] (Table 4). None of these trials detected a significant survival benefit for particle therapy. The first four studies looked at neutrons, and the fifth study by Pickles et al. randomized 81 patients to either 60 Gy in 30 fractions with photons or pion therapy to 33–34.5 Gy where the median survival was 10 months in both groups [56]. In the randomized, dose-searching study by the RTOG [17], 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 [24] 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. [17], all patients who died had evidence of residual brain tumour. None had signs of radiation-related morbidity. The subsequent trial by Duncan et al. [16] was discontinued prematurely as a result of neutron morbidity. In this study, four of nine patients treated by neutrons had evidence at autopsy of radiation-induced brain damage and all had residual malignant glioma.

3.11. 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 would deserve further investigation. The
two major classes of compounds investigated to date are hypoxic cell sensitzers and halogenated pyrimidines.

3.11.1. Hypoxic cell sensitizers

Intra-operative in vivo measurements and examinations of patients fluoride-18-fluoromisonidazole PET have demonstrated the presence of hypoxic regions in glioblastomas [31,58,77]. It has been well established in the laboratory that hypoxic cells are significantly more resistant to radiation than oxic cells by an order of 2.5 to 3. 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 [75]. However, the patient numbers were small, and the median survival of 4 months with radiation alone was considerably less than seen in most other studies. Since then, there have been 11 additional randomized studies (involving 1605 patients) which have not shown any benefit from the addition of nitroimidazoles to various combinations of radiotherapy and chemotherapy [3,17,18,26,46,49,51,59,67,73,76] (Table 5).

There have been two meta-analyses examining the potential value of hypoxic cell sensitizers in the treatment of malignant gliomas [30,52]. Overgaard pooled the same 12 randomized trials (13 comparisons) shown in Table 5 and reported a mortality OR of 1.04 (95% CI, 0.82–1.26; $P = 0.71$) [52]. Overgaard did not describe the search methods or the methods used to pool the data, and no quality assessment of the included studies was reported. In contrast, Huncharek [30] 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, two independent reviewers extracted the data. Huncharek pooled 1-year survival data from nine randomized trials using misonidazole in the treatment of high-grade astrocytoma [3,17,18,20,46,49,67,73,76]. Of note, two reports of the

<table>
<thead>
<tr>
<th>Study [Ref.]</th>
<th>Treatment</th>
<th>No. of patients randomized (analyzed)</th>
<th>Median survival (months) sensitizer</th>
<th>Median survival (months) radiation</th>
<th>Overall survival P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urtasun et al., 1976 [75]</td>
<td>Metronidazole</td>
<td>29</td>
<td>7</td>
<td>4</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>Urtasun et al., 1982 [76]</td>
<td>Metronidazole</td>
<td>36</td>
<td>5</td>
<td>6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sack et al., 1982 [59]</td>
<td>Misonidazole</td>
<td>42</td>
<td>7</td>
<td>6</td>
<td>n.s.</td>
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<tr>
<td>Stadler et al., 1984 [73]</td>
<td>Misonidazole</td>
<td>45</td>
<td>13.8</td>
<td>9.8</td>
<td>n.s.</td>
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<tr>
<td>Hatlevoll et al., 1985 [26]</td>
<td>Misonidazole</td>
<td>244</td>
<td>10</td>
<td>10</td>
<td>n.s.</td>
</tr>
<tr>
<td>Nelson et al., 1986 [49]</td>
<td>Misonidazole</td>
<td>146</td>
<td>11.5</td>
<td>12.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Okkan et al., 1988 [51]</td>
<td>Ornidazole</td>
<td>40</td>
<td>15</td>
<td>10</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

* n.s., not statistically significant; WBRT, whole brain radiation therapy.
same study were included [20,67] as well as a preliminary report of the RTOG study by Nelson et al. rather than the final report [49]. The results demonstrated no statistically significant difference in 1-year survival for misonidazole compared with the control (OR, 0.92; 95% CI, 0.77–1.09; P value not stated) [30]. There was no significant heterogeneity. Huncharek concluded that ‘misonidazole treatment is associated with an approximately 8% improved 1-year survival compared with non-misonidazole treatment arms’, which does not follow from the nonsignificant results of the meta-analysis.

3.11.2. Halogenated pyrimidines

The halogenated pyrimidines 5-bromodeoxyuridine (BUdR) and 5-iododeoxyuridine (I UdR) 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 [55]. There was no significant improvement seen with the use of BUdR for patients with glioblastoma. As a result of this 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 1-year survival rate for radiotherapy, PVC, and BUdR was 68 versus 82% for radiotherapy plus PVC (one-sided P = 0.96) [57].

3.12. 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 last few years [6,7,21,35,40,42,44,45,61,65,68]. The patient population in these studies is selected with no concurrent randomized cohorts, and as such one cannot comment on the possible advantage of this approach. Curran et al. [13] demonstrated the impact of favourable prognostic factors on radiosurgery eligible patients on a data set of 778 patients with malignant gliomas who were treated on a hyperfractionated radiation therapy protocol. Median survival for 89 radiosurgery eligible patients versus 643 radiosurgery ineligible patients was 14.4 versus 11.7 months, respectively (P = 0.047), but the median survival for 544 radiosurgery ineligible patients with a KPS > 60 was 12.1 months, not statistically inferior to the radiosurgery eligible patients (P = 0.21) [13].

3.13. 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 [41]. Many of these clinical late effects can be related to white matter changes noted on magnetic resonance imaging and computerized tomography [9,11]. 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 [10].

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 paper deal with strategies to increase the radiation dose either directly or through mechanisms of radiation sensitization. Inherent in these 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 these tumours are associated with large zones of necrosis which 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 that are related to the more aggressive neoplasms discussed in this paper, and for whom the same types of experimental treatments have been attempted [39]. 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 [39]. The survival rates for these three cohorts were 3.0, 2.3, 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.

4. Discussion

Many of the studies included in this 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 5–10
years, such that results and recommendations based on these older data may no longer be pertinent. Nevertheless, until new evidence emerges that revisits many of the issues raised in this review, the DSG agreed not to develop new recommendations.

Additionally, most of these 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 this information available to be able to make informed choices amongst the therapeutic options. It is strongly recommended that future studies in patients with brain tumours include measures of toxicity and quality of life.

4.1. Conventional radiation

Post-operative radiotherapy as an appropriate recommendation for patients is well supported by randomized studies and remains standard therapy. 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 [33,63].

In view of the fact that greater than 90% of recurrences occur at the primary site or immediately adjacent to the original enhancing tumour, most centres and all on-going 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.

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 statistically significant benefit for the higher dose [4]. The joint study of the RTOG/ECOG did not show any advantage of 70 Gy over 60 Gy [48]. There are no randomized data examining 50 or 54 Gy versus 60 Gy in this 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 [37]. Since no randomized studies of dose escalation have shown any benefit compared with conventional doses in the range of 50–60 Gy, the Neuro-Oncology DSG felt that doses in the range of 50–60 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 which remains incurable. Accordingly, the evidence would support the use of post-operative radiotherapy to a total dose in the range of 50–60 Gy utilizing conventional fractionation.

4.2. 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 50–60 Gy.

One randomized study of accelerated fractionation compared with conventional fractionation has been performed and it demonstrated no survival difference. The survival data from the reported cohorts of patients are within the range of expected results with conventional fractionation. However, these shorter regimens have been well tolerated and have not shown any increased incidence of late sequelae. This 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 45–50 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 have a short life expectancy despite receiving radiation therapy, namely patients with adverse prognostic factors (older age and/or a poor performance status). The doses utilized for these patients ranged from 30 Gy in 6 fractions to 42 Gy in 14 fractions [2,19,28,34,74]. This 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 5-week course of treatment [22]. While there was no significant survival difference overall, the author reported a survival advantage at 2 years favouring the hypofractionated arm for the subset of 44 patients with glioblastoma. This is an interesting observation, which would require further study, but differentiating anaplastic astrocytoma from glioblastoma is well known to be difficult [50]. The hypofractionated dose utilized in the study by Glinski [22] given over 3 months is an extremely unusual fractionation, and one that the DSG does not recommend. Based on these 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 4-week improvement in median survival over brachytherapy alone, the modest gain may not justify the added cost and morbidity associated with this approach.
Studies did not demonstrate any benefit for the use of particle therapy over conventional photon radiotherapy for patients with malignant glioma. These modalities remain as investigational approaches.

4.3. 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 these 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. This approach remains within the domain of experimental therapy.

5. Conclusions

Post-operative external beam radiotherapy is recommended as standard therapy for patients with malignant glioma. 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. Radiation dose intensification and radiation sensitiser approaches are not recommended as standard care. For patients older than age 70, preliminary data suggest that the same survival benefit can be achieved with less morbidity using a shorter course of radiotherapy. Since the outcome following conventional radiotherapy is so poor for patients older than age 70 with a poor performance status, supportive care alone is a reasonable therapeutic option in these patients. 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.

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