Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials

Glioma Meta-analysis Trialists (GMT) Group*

Summary

Background Trials on the effect of systemic chemotherapy on survival and recurrence in adults with high-grade glioma have had inconclusive results. We undertook a systematic review and meta-analysis to assess the effects of such treatment on survival and recurrence.

Methods We did a systematic review and meta-analysis using updated data on individual patients from all available randomised trials that compared radiotherapy alone with radiotherapy plus chemotherapy. Data for 3004 patients from 12 randomised controlled trials were included (11 published and one unpublished).

Findings Overall, the results showed significant prolongation of survival associated with chemotherapy, with a hazard ratio of 0.85 (95% CI 0.78–0.91, p<0.0001) or a 15% relative decrease in the risk of death. This effect is equivalent to an absolute increase in 1-year survival of 6% (95% CI 3–9) from 40% to 46% and a 2-month increase in median survival time (1–3). There was no evidence that the effect of chemotherapy differed in any group of patients defined by age, sex, histology, performance status, or extent of resection.

Interpretation This small but clear improvement in survival from chemotherapy encourages further study of drug treatment of these tumours.

Lancet 2002; 359: 1011–18

Introduction

Malignant gliomas are among the most devastating of cancers, commonly producing profound and progressive disability and leading to death in most cases. They are difficult to diagnose and challenging to treat. Incidence peaks in children and at age 50–60 years.1 These tumours are therefore a major cause of mortality in a young population, and improvement of survival by even a moderate amount could potentially result in many years of life saved. The infiltrating nature of high-grade glioma makes complete resection virtually impossible, even when possible resection can be associated with severe neurological damage. Thus, standard treatment generally consists of cytoreductive surgery followed by radiotherapy. However, prognosis remains poor, with a median survival time of 9 months and only 3–10% of patients surviving to 2 years.2 Over a period of almost 30 years, several randomised trials have explored the use of adjuvant chemotherapy, with research mostly focusing on nitrosoureas, which are used because they are lipid soluble and cross the blood-brain barrier. Most of these trials have been small, and many have randomised multiple treatments within the trial. Not surprisingly, therefore, most have shown inconclusive results and there is consequently no international consensus on the value of chemotherapy in this setting.

Combination of the results of trials in a meta-analysis increases statistical power and may provide sufficient information to show any survival benefit more reliably. Two meta-analyses based on summary data extracted from trial reports have been published.3,4 However, these have several limitations and potential biases. Each identified only a proportion of currently relevant trials and included some that used pseudo-random methods of allocation, which are liable to bias.5 The meta-analyses were limited to published trials, thereby being susceptible to publication bias,6 and many of the trials excluded substantial proportions of patients (on average 10–15%) from their published analyses, potentially introducing further bias. There is strong evidence that meta-analyses based on data extracted from published reports can give different results from those based on updated data on individual patients.7,8

We therefore initiated a systematic review and a meta-analysis based on individual patient data to collect, validate, and reanalyse trial data on all randomised patients from all relevant trials. This approach has many advantages.9 In particular, it permits time-to-event analyses, which are extremely important in a disease such as malignant glioma, for which prolongation of survival rather than cure is expected. It also allows analyses to assess whether chemotherapy may be more or less effective in different subgroups of patients. The meta-analysis was initiated and coordinated by the UK Medical Research Council Clinical Trials Unit and done by the Glioma Meta-analysis Trialists (GMT) group.

Methods

Inclusion criteria

This systematic review and meta-analysis followed a detailed, prespecified protocol, which set out the objectives, inclusion criteria for trials, data to be collected, and analyses to be done (available on request).

*Members listed at the end of the paper

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**Identification of trials**

To avoid publication bias, both published and unpublished trials were included. Computerised bibliographic searches of Medline and CancerLit used a version of the Cochrane Collaboration optimum search strategy. This strategy was also modified and used to search Embase. These searches were supplemented by hand-searching of the reference lists of identified trials and bibliographies of relevant books and review articles. The trials registers of the US National Cancer Institute PDQ (Physicians Data Query) Clinical Protocols and UK Coordinating Committee for Cancer Research were also searched so that both completed and current trials could be identified. All trialists who took part in the meta-analysis were asked to help identify trials. Initial searches were completed for the period up to and including June 1, 1997. Medline and the trial registers were researched in June, 1999, and again in December, 2000, for any material that had appeared since our final analyses were done during November, 2000. All titles identified by search strategies were assessed for relevance independently by two reviewers. Abstracts were downloaded for all titles of potential relevance, and full papers were obtained for all abstracts judged potentially relevant. Where there was uncertainty about the eligibility of a trial or particular

<table>
<thead>
<tr>
<th>Ref</th>
<th>Accrual dates</th>
<th>Treatment groups included</th>
<th>Eligible histology</th>
<th>Eligible surgery</th>
<th>Delay (weeks)</th>
<th>Radiotherapy details</th>
<th>Chemotherapy details</th>
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<tbody>
<tr>
<td>26</td>
<td>1969–72</td>
<td>Anaplastic glioma</td>
<td>Definitive surgery</td>
<td>Whole brain; 50–60 Gy; 30–35 fractions; 6–7 weeks</td>
<td>6</td>
<td>Carmustine 80 mg/m²×3 intravenously, every 6–8 weeks</td>
<td>193</td>
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<tr>
<td>27</td>
<td>1971–73</td>
<td>High-grade astrocytoma</td>
<td>Resection, biopsy</td>
<td>Whole brain; 40–45 Gy; 25 fractions; 4–5 weeks; cobalt-60</td>
<td>2</td>
<td>Carmustine 80 mg/m²×3 intravenously, every 6–8 weeks; lomustine 130 mg/m² orally, every 6–8 weeks</td>
<td>20§</td>
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<td>1972–76</td>
<td>Glioblastoma multiforme</td>
<td>Total or subtotal resection</td>
<td>Tumour and margin; 50 Gy; 25–30 fractions; 5 weeks</td>
<td>2</td>
<td>Carmustine 80 mg/m²×3 intravenously, every 6–8 weeks; methyl lomustine 125 mg/m² orally, every 8 weeks; dacarbazine 150 mg/m²×5 intravenously, every 4 weeks</td>
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<td>30</td>
<td>1974–79</td>
<td>Astrocytoma, grade III/IV (Kernohan)</td>
<td>Resection, biopsy</td>
<td>Whole brain; 60 Gy; 35 fractions; 7 weeks; megavoltage</td>
<td>4</td>
<td>Carmustine 80 mg/m²×3 intravenously, every 6–8 weeks</td>
<td>511</td>
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<tr>
<td>28</td>
<td>1972–75</td>
<td>Malignant glioma</td>
<td>Definitive surgery</td>
<td>Whole brain; 60 Gy; 30–35 fractions; 6–7 weeks;</td>
<td>3</td>
<td>Carmustine 80 mg/m²×3 intravenously, every 6–8 weeks</td>
<td>355</td>
</tr>
<tr>
<td>32</td>
<td>1974–78</td>
<td>Malignant glioma</td>
<td>Definitive surgery</td>
<td>Tumour and margin; 60 Gy; 30–35 fractions; 6–7 weeks</td>
<td>3</td>
<td>Carmustine 80 mg/m²×3 intravenously, every 8 weeks: procarbazine 150 mg/m²×28 days, every 8 weeks</td>
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</tr>
<tr>
<td>31</td>
<td>1975–78</td>
<td>Malignant glioma</td>
<td>Optimum resection</td>
<td>Tumour and margin; 55–60 Gy; 30 fractions; 6 weeks; betatron, telecobalt, linear accelerator</td>
<td>4</td>
<td>Carmustine 80 mg/m²×3 orally, every 6–8 weeks</td>
<td>116</td>
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<tr>
<td>33</td>
<td>1978–81</td>
<td>Glioblastoma; malignant astrocytoma grade III (WHO/Zulch)</td>
<td>At least subtotal resection</td>
<td>Tumour and margin; 51 Gy; 25–30 fractions; 5–6 weeks; cobalt-60</td>
<td>4</td>
<td>Mitolactol 400 mg/m², every 5 days during radiotherapy, with 1 month rest then repeat; mitolactol 400 mg/m², every 5 days during radiotherapy, with 6 weeks rest then (day 1) lomustine 100 mg/m² followed by dacarbazine 200 mg/m², every 5 days×7</td>
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<tr>
<td>34</td>
<td>NK</td>
<td>Glioma (high and low grade)† †</td>
<td>Resection</td>
<td>Tumour and margin; 60 Gy; 30 fractions; 6 weeks;</td>
<td>3</td>
<td>Lomustine 100 mg/m² orally, every 6–8 weeks</td>
<td>125</td>
</tr>
<tr>
<td>35</td>
<td>1986–97</td>
<td>Malignant astrocytoma, glioblastoma, ependymoma, oligodendroglioma</td>
<td>Resection, biopsy</td>
<td>Tumour and margin; 55–60 Gy; 30 fractions; 6 weeks; betatron, telecobalt, linear accelerator</td>
<td>3</td>
<td>Before radiotherapy: lomustine 130 mg/m² orally, plus epipodophyllotoxin 100 mg/m² intravenously, every 6 weeks 3 courses</td>
<td>235</td>
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<tr>
<td>36</td>
<td>1989–91</td>
<td>Anaplastic astrocytoma, glioblastoma</td>
<td>Resection, stereotactic biopsy</td>
<td>Tumour and margin; 60 Gy; 30–35 fractions; 6–7 weeks;</td>
<td>4</td>
<td>Dacarbazine 700 mg/m²×6 orally during radiotherapy, then lomustine 150 mg/m² intravenously; dacarbazine 1000 mg/m² orally, every 6 weeks</td>
<td>270</td>
</tr>
</tbody>
</table>

**ARTICLES**

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The times to event hazard ratios for individual trials and overall pooled hazard number of deaths and variance were used to calculate the overall risk of an event for the patients allocated adjuvant chemotherapy compared with those allocated no chemotherapy. To investigate the effects of chemotherapy within subgroups of patients, similar stratified analyses were done. Analyses were done for each prespecified category, for example, comparing treatment and control for male and female patients within each individual trial. These results were then combined to give overall hazard ratios for male and female patients. Results are also presented as absolute differences at 1 year and 2 years, calculated from the overall hazard ratios and event rate in the control group. Absolute effects for different types of patients defined by categories used in our subgroup analyses were calculated from the overall hazard ratio and event rates in the surgery-alone group for each subgroup. CIs for absolute differences were calculated from the baseline event rate and the hazard ratio.

Role of the funding source
The sponsors of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Preliminary searches identified 24 randomised trials that compared surgery plus radiotherapy with the same standard treatment plus adjuvant cytotoxic chemotherapy in adult patients with high-grade glioma. Five of these were found to be ineligible: two allocated treatments by an alternating sequence,17 and one was confounded by the use of hyperbaric oxygen in the control group only.18 One trial19 had several treatment groups within a trial, it was discussed and resolved by consensus within the project secretariat, and ratified by the GMT group at a meeting held in July, 1999.

For trials with several treatment groups, the eligibility of each individual group was assessed and only those relevant were included.

Data collection and endpoints
Up-to-date information on date of randomisation, survival status, recurrence status, and date of last follow-up was sought, as were details of treatment allocated, age, sex, histological cell type, performance status, and extent of tumour resection. To avoid potential bias, information was requested for all randomised patients, including those who had been excluded from the investigators’ original analyses. All data were thoroughly checked for consistency, plausibility, and integrity of randomisation and follow-up. Any queries were resolved and the final database entries verified by the responsible trial investigator or statistician. Overall survival was defined as the time from randomisation until death (from any cause). Data for surviving patients were censored on the date of last follow-up. Progression-free survival was defined as the time from randomisation until progression or death (by any cause), whichever happened first. Data for patients alive without progression were censored on the date of last follow-up.

Analysis and statistics
All analyses were done by intention to treat. Survival analyses were stratified by trial, and the log-rank expected number of deaths and variance were used to calculate hazard ratios for individual trials and overall pooled hazard ratios by the fixed-effect model.12 Thus, the times to event (progression or death) for individual patients were used in our subgroup analyses were calculated from the overall hazard ratio and event rates in the surgery-alone group for each subgroup. CIs for absolute differences were calculated from the baseline event rate and the hazard ratio. χ² heterogeneity tests20 were used to test for gross statistical heterogeneity across trials. χ² tests for interaction or trend were used to test for differences in outcome between subsets of trials or between subgroups of patients. Survival curves are presented as simple (non-stratified) Kaplan-Meier curves. All p values quoted are two-sided.

Table 2: Characteristics of unavailable eligible trials

<table>
<thead>
<tr>
<th>Ref</th>
<th>Accrual dates</th>
<th>Relevant treatment groups</th>
<th>Eligible histology</th>
<th>Eligible surgery</th>
<th>Delay*</th>
<th>Radiotherapy details</th>
<th>Chemotherapy details</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK</td>
<td>252</td>
<td>All</td>
<td>Astrocytoma, grade III/IV</td>
<td>NK</td>
<td>2</td>
<td>Whole brain; 50 Gy; 25 fractions; 5 weeks; or 26 Gy; 10 fractions; 5 weeks, split course, 3 weeks rest then repeat; cobalt-60 or 4 MV linear accelerator</td>
<td>Dianhydrogalactitol 25 mg/m²; ×5 intravenously; every 5 weeks for year 1 and 10 weeks thereafter</td>
</tr>
<tr>
<td>1970–72</td>
<td>2/3§</td>
<td>All</td>
<td>Astrocytoma grade III/IV</td>
<td>Resection, biopsy</td>
<td>2</td>
<td>Whole brain; 50 Gy; 25–28 fractions; every 30–39 days; cobalt-60 or 4 or 6 MV linear accelerator</td>
<td>Lamotrigine 130 mg/m² orally, every 8 weeks</td>
</tr>
<tr>
<td>1974–78</td>
<td>2/3§</td>
<td>All</td>
<td>Astrocytoma grade III/IV</td>
<td>Resection, biopsy</td>
<td>4</td>
<td>Whole brain; 45 Gy; 25 fractions; 5 weeks; megavoltage</td>
<td>Bleomycin 15 mg intravenously ×12 days</td>
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<tr>
<td>22</td>
<td>NK</td>
<td>All</td>
<td>Malignant glioma (not requiring steroids)</td>
<td>Optimum resection</td>
<td>3</td>
<td>55–60 Gy; 30 fractions; 6 weeks; betatron or telecobalt</td>
<td>Lamotrigine 130 mg/m² orally, every 6 weeks</td>
</tr>
<tr>
<td>22</td>
<td>NK</td>
<td>All</td>
<td>Malignant glioma (requiring steroids)</td>
<td>Optimum resection</td>
<td>3</td>
<td>55–60 Gy; 30 fractions; 6 weeks; betatron or telecobalt</td>
<td>Lamotrigine 130 mg/m² orally, every 6 weeks</td>
</tr>
<tr>
<td>234</td>
<td>NK</td>
<td>All</td>
<td>Astrocytoma grade III, glioblastoma multiforme</td>
<td>Partial resection</td>
<td>2</td>
<td>Whole brain; 50–60 Gy; 25–30 fractions; 5–6 weeks; cobalt-60 or megavoltage</td>
<td>Nimustine 100 mg/m², every 4–5 weeks, two courses</td>
</tr>
<tr>
<td>211</td>
<td>1979–82 All**</td>
<td>All</td>
<td>Astrocytoma, grade III/IV (WHO/Zülieh)</td>
<td>Large resection</td>
<td>4</td>
<td>Whole brain; 40 Gy; 10 fractions; Lamotrigine 120 mg/m² orally, every 6 weeks</td>
<td>280</td>
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</tbody>
</table>

patients who had been excluded from the original published randomised trials. Data were gathered for 210 of the 253 trial by the EORTC Brain Group), which included 3004 unable to collaborate. No further relevant trials either 12 randomised controlled trials (and one unpublished trial), although the glioma, treatment related, or other) were provided for eight patients were not evenly distributed across treatment groups, so the main analyses were done both with and without this trial.

Design features of all eligible trials are shown in tables 1 and 2. Among the included trials, total radiotherapy doses ranged from 40 Gy to 60 Gy given in 25 to 35 fractions. In four trials, whole-brain irradiation was delivered and in eight the tumour plus margins were irradiated. The maximum planned delay between surgery and radiotherapy/chemotherapy ranged from 2 to 6 weeks, and in all but one trial randomisation was done before radiotherapy. All trials included at least one nitrosourea compound, given as a single agent or in combination with other drugs. Chemotherapy regimens and planned drug doses are given in tables 1 and 2.

Although trials were able to provide most of the data on the patients’ baseline characteristics that we requested, some data were unavailable. Information on age, sex, histology, and extent of resection was provided for eight patients. Because the missing patients were few and distributed evenly across treatment groups, the trial was included. In another trial, data had to be read from archived computer printouts, and we were unable to retrieve information on 19 patients because their data had become detached from the end of the listing. These missing patients were not evenly distributed across treatment groups, so the main analyses were done both with and without this trial.

For one trial, we were unable to obtain information from eight patients. Because the missing patients were few and distributed evenly across treatment groups, the trial was included. In another trial, data had to be read from archived computer printouts, and we were unable to retrieve information on 19 patients because their data had become detached from the end of the listing. These missing patients were not evenly distributed across treatment groups, so the main analyses were done both with and without this trial.

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lower radiotherapy doses (less than 60 Gy), with hazard ratios of 0.88 and 0.77 respectively (interaction p=0.11). A further analysis excluding the trial that had itself suggested an interaction between radiotherapy dose and effect of chemotherapy also showed no evidence of differential results by radiotherapy dose, with hazard ratios of 0.83 for trials using 60 Gy and 0.79 for those using less than 60 Gy (interaction p=0.68). A sensitivity analysis based on only those patients with glioblastoma multiforme and anaplastic astrocytoma (93% of those with known histology) gave a very similar estimate to the main result (hazard ratio 0.83 [0.76–0.90], p<0.0001).

Information on disease progression was available from eight trials (2022 patients). 1859 events were recorded. The results showed a similar pattern to those for survival. The overall hazard ratio of 0.83 (0.75–0.91; figure 3) indicated a significant (p<0.0001) 17% reduction in the risk of progression or death. This is equivalent to an absolute benefit of 5% (2–8) at 2 years, increasing progression-free survival from 10% to 15%. Median progression-free survival was increased by 1.5 months (0.5–2.5) from 6 months to 7.5 months.

Analyses were undertaken to investigate whether there was evidence of a differential effect of chemotherapy in predefined subgroups of patients. For survival, there was no evidence that chemotherapy was differentially effective in any group of patients defined by age, sex, histology, performance status, or extent of resection (figure 4).

Because information was not available from seven trials (683 patients), we did a separate analysis based on data from published reports of six trials from which appropriate data could be extracted. This analysis used numbers of patients who had died by 2 years to calculate an odds ratio at that time. It gave results similar to those of our analysis of individual patients’ data (odds ratio 0.92 [0.79–1.09]).

**Discussion**

At the outset of this project, despite enrolment of more than 3500 patients in randomised trials, whether chemotherapy was effective in treatment of high-grade glioma remained unclear. Current clinical practice varies nationally and internationally. The aim of this systematic review and meta-analysis was to provide a comprehensive, reliable, and up-to-date summary of the

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**Table:**

<table>
<thead>
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<th>Ref</th>
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<tr>
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<td>30</td>
<td>316/344</td>
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<td>98.87</td>
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<td>54/61</td>
<td>-1.00</td>
<td>25.14</td>
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<td>57/59</td>
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<td>100/120</td>
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<td>318/335</td>
<td>-8.30</td>
<td>157.97</td>
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<tr>
<td>36</td>
<td>121/135</td>
<td>-25.69</td>
<td>58.34</td>
</tr>
<tr>
<td>Total</td>
<td>1035/1136</td>
<td>-80.69</td>
<td>423.83</td>
</tr>
</tbody>
</table>

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**Figure 3:** Hazard ratio plot for progression-free survival

χ²=15.36, p=0.0001; heterogeneity χ²=20.07, p=0.005.

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**Figure 2:** Kaplan-Meier curve for survival
bias associated with trial availability; for example, in the analysis of individual patient data is useful. In results from the unavailable trials with those included for the missing trials. Although there are many potential of the total randomised evidence, we did a comparative to 13%, whereas that for patients with anaplastic with glioblastoma multiforme is increased from 9% for example, that 2-year survival for individuals in outcome rates. Baseline survival and corresponding are likely to translate to different absolute improvements in overall risk of death with chemotherapy. However, is that he or she is likely to have around 15% reduction in their likely survival time, if only by a modest amount. For the primary endpoint of survival, there was clear evidence of a beneficial effect of adjuvant chemotherapy. Although many trials were completed some years ago and did not include central pathology review, there was no indication that the results were driven by inclusion of chemosensitive tumours such as oligodendrogliomas. A sensitivity analysis based on only the anaplastic astrocytoma and glioblastoma multiforme tumours gave results very close to the main result. In addition, the results of subgroup analyses showed a benefit of chemotherapy irrespective of histology. We have no reason to believe that the results would not be applicable to present-day patients with a confirmed diagnosis of glioblastoma. Further supplementary analyses by age, sex, performance status, and extent of tumour resection also gave no indication that the relative effect of chemotherapy varied in the different subgroups included in the meta-analysis. Thus, the best estimate for any individual patient is that he or she is likely to have around 15% reduction in overall risk of death with chemotherapy. However, since the underlying outlooks for different categories of patients vary substantially, these relative effects are likely to translate to different absolute improvements in outcome rates. Baseline survival and corresponding absolute increases are shown in table 4. This shows, for example, that 2-year survival for individuals with glioblastoma multiforme is increased from 9% to 13%, whereas that for patients with anaplastic astrocytoma is increased from 31% to 37%.

Because data were not available from around 19% of the total randomised evidence, we did a comparative analysis on the basis of data presented in publications for the missing trials. Although there are many potential problems and biases with this approach, comparison of results from the unavailable trials with those included in the analysis of individual patient data is useful. In particular, we can explore whether there is any obvious bias associated with trial availability; for example, did we have access only to the positive trials? The results of this analysis of survival at 2 years showed broadly similar results to our analysis of individual patient data, indicating efficacy of chemotherapy. Thus, we can be reasonably confident that, had we successfully obtained the missing data, the results of our analysis would not have been substantially altered.

Undoubtedly, there are design differences in the trials included in the meta-analysis, especially in the radiotherapy regimens and techniques used. A possible explanation of the results is that rather than giving an additional advantage, chemotherapy is simply making up for inadequate radiotherapy. However, there was no compelling evidence that the effect of chemotherapy was moderated by radiotherapy total dose. The hazard ratio for trials delivering 60 Gy did not differ significantly from that of the remainder of trials and it was very similar to the overall hazard ratio. Thus, the effect of chemotherapy was apparent in trials delivering radiotherapy doses similar to those widely used in current clinical practice, and there is no strong evidence that chemotherapy is merely compensating for inadequate radiotherapy techniques.

Whether the benefits of chemotherapy detected in the meta-analysis are clinically worthwhile remains open to interpretation. The benefit is likely to vary with the clinical situation and individual patient’s and family’s preference. Tolerability of treatment and quality of life, including cognitive impairment, are major issues for patients who will survive for only a short time after their treatment has finished. Few trials included in this meta-analysis formally measured quality of life or undertook cognitive function tests in ways that would allow data to be combined in a meta-analysis. We are therefore unable to assess quality of life. However, in decisions about treatment, the interpretation of such information is likely to be affected by many personal beliefs and preferences, so interpretation of these data in isolation may not be particularly helpful. In this respect, the literature, though not a novel treatment, are fairly well tolerated and easily administered, so they may be of practical use in the clinic for those individuals who wish to extend their likely survival time, if only by a modest amount.

The clear effect observed in this comprehensive review of the data provided by the 45 trials delivering radiotherapy doses similar to those used in current clinical practice is that chemotherapy is beneficial in extending survival for individuals with glioblastoma multiforme. In addition, this meta-analysis shows that the benefit of chemotherapy is independent of histology, extent of tumour resection, age, sex, performance status, and extent of tumour resection. These findings are consistent with the results of the individual patient data analysis, which showed a significant benefit of chemotherapy for all subgroups, including those with anaplastic astrocytoma, glioblastoma multiforme, and oligodendrogliomas. The results of this meta-analysis are consistent with the findings of the individual patient data analysis, and provide evidence that chemotherapy is beneficial in extending survival for individuals with glioblastoma multiforme.
does show that high-grade gliomas can respond to chemotherapy and that further research into newer chemotherapy methods and methods of delivery is justified. The size of the benefit and remaining uncertainty about quality of life mean that some clinical trialists would consider radiotherapy alone to be a justified standard therapy, whereas others might believe that the appropriate standard therapy should now include a nitrosourea. Both camps are likely to agree that the small but clear improvement in survival from chemotherapy encourages further study of drug treatment of these tumours.

Contributors
All aspects of the meta-analysis were carried out under the auspices of the GMT group. D Afra, Bar, G Bonadonna, J W Curran, S B Green, J Hildebrand, C B Scott, W Shapiro, D Thomas, T Trojanowski, R Ursin, and M D Walker collated and supplied the individual patients’ data, contributed to the discussions of the results, and commented on drafts of the report. The project was organised by the secretariat, S Burdett, M K B Parmar, R L Souhami, S P Stenning, and L A Stewart, who were responsible for formulating the question, developing the protocol, receiving, checking, and analysing data. The project was managed by S Burdett. The report was drafted by L A Stewart and S Burdett with detailed input from R L Souhami and S Stenning.

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Conflict of interest statement
None declared.

Acknowledgments
The UK Medical Research Council funded the coordination of the meta-analysis and the collaborators’ meeting. We thank all the patients who took part in the trials and contributed to this research. The meta-analysis would not have been possible without their participation or without the collaborating institutions that kindly supplied their trial data. We also thank Richard Kaplan and the US National Cancer Institute for supporting data retrieval by the Radiation Therapy Oncology Group (RTOG), Jayne Tierney for comments and assistance at all stages of the project, and Claire Vale and Janet Darbyshire for helpful comments on the report.

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