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 Data for 3004 patients from 12 randomised controlled trials were included (11 published and one unpublished).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

*Members listed at the end of the paper

Correspondence to: Dr L A Stewart, Meta-analysis Group, MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA, UK (e-mail: ls@ctu.mrc.ac.uk)

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 5–10% 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).

Ref	Accrual dates	Treatment groups included	Eligible histology	Eligible surgery	Delay*	Radiotherapy details	Chemotherapy details	n†
26	1969–72	2/4‡	Anaplastic glioma	Definitive surgical resection	6	Whole brain; 50–60 Gy; 30–35 fractions; 6–7 weeks	Carmustine 80 mg/m²×3 intravenously, every 6–8 weeks	193
27	1971–73	2/3‡	High-grade astrocytoma	Resection, biopsy	2	Whole brain; 40–45 Gy; 25 fractions; 4–5 weeks; cobalt-60	Lomustine 130 mg/m² orally, every 6 weeks	20§
29	1972–76	All	Glioblastoma multiforme	Total or subtotal resection	2	Tumour and margin; 50 Gy; 25–30 fractions; 5 weeks	Carmustine 80 mg/m²×3 intravenously, every 6–8 weeks; lomustine 130 mg/m² orally, every 6–8 weeks	105
30	1974–79	3/4‡	Astrocytoma, grade III/IV (Kernohan)	Resection, biopsy	4	Whole brain; 60 Gy; 35 fractions; 7 weeks; megavoltage	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‖	511
28	1972–75	3/4‡	Malignant glioma	Definitive surgery	3	Whole brain; 60 Gy; 30–35 fractions; 6–7 weeks; megavoltage	Methyl lomustine 220 mg/m² orally, every 6–8 weeks; carmustine 80 mg/m²×3 intravenously, every 6–8 weeks	355
32	1974–78	2/4¶	Malignant glioma	Definitive surgery	3	Tumour and margin; 60 Gy; 30–35 fractions; 6–7 weeks	Carmustine 80 mg/m²×3 intravenously, every 8 weeks: procarbazine 150 mg/m²×28 days, every 8 weeks	309
31	1975–78	**	Malignant glioma	Optimum resection	4	Tumour and margin; 55–60 Gy; 30 fractions; 6 weeks; betatron, telecobalt, linear accelerator	Lomustine 130 mg/m² orally; epipodophyllotoxin 60 mg/m² intravenously, every 6 weeks	116
33	1978–81	All	Glioblastoma; malignant astrocytoma grade III (WHO/Zulch)	At least subtotal resection	4	Tumour and margin; 51 Gy; 25–30 fractions; 5–6 weeks; cobalt-60	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	91
34	NK	All	Glioma (high and low grade)††	Resection	3	Tumour and margin; 60 Gy; 30 fractions; 6 weeks; cobalt-60	Lomustine 100 mg/m² orally, every 6–8 weeks	125
Un-publ	1982–87	All	Malignant astrocytoma, glioblastoma, ependymo blastoma, oligondendroglioma	Optimum resection	3	Tumour and margin; 55–60 Gy; 30 fractions; 6 weeks; betatron, telecobalt, linear accelerator	Before radiotherapy: lomustine 130 mg/m² orally, plus epipodophyllotoxin 100 mg/m² intravenously, every 6 weeks 3 courses	235
35	1986–97	All	Astrocytoma grade III/IV (WHO/Zulch)	Resection, biopsy	6	Tumour and margin; 45 Gy; 20 fractions; 4 weeks; or 60 Gy; 30 fractions; 6 weeks; or 55 Gy; 34 twice-daily fractions‡‡	Lomustine 100 mg/m²; procarbazine 100 mg/m² orally×10; vincristine 1·5 mg/m², every 6 weeks	674
36	1989–91	All	Anaplastic astrocytoma, glioblastoma	Resection, stereotactic biopsy (stratified)	4	Tumour and margin; 60 Gy; 30–35 fractions; 6–7 weeks; cobalt-60 or megavoltage	Dacarbazine 700 mg/m²×6 orally during radiotherapy, then carmustine 150 mg/m² intravenously; dacarbazine 1000 mg/m² orally, every 6 weeks	270

NK=not known. *Maximum delay after surgery (weeks). †Number of patients randomised. ‡Remaining groups not relevant. §Data from eight patients not available. ¶Control group were assigned surgery, radiotherapy, and prednisolone; treatment group, radiotherapy, prednisolone, and carmustine; the other two treatment groups (surgery, radiotherapy, and carmustine or procarbazine) were judged ineligible because they differed from the control group not only by addition of chemotherapy but also lack of prednisolone. ‖Doses initially 150 mg/m² and 175 mg/m² but reduced owing to severe toxicity. **Includes only patients in first randomisation. Patients with recurrence entered at time of second randomisation were not included. ††Patients with low-grade disease not included in meta-analysis. ‡‡Institutions chose their standard radiotherapy schedule (60 Gy, 501 patients; 45 Gy, 135 patients; accelerated 55 Gy, 38 patients).

Table 1: **Characteristics of available eligible trials**

To be included in the meta-analysis, trials had to be properly randomised. Treatment had to be assigned in such a way that the allocation could not have been known beforehand (eg, allocation by date of birth was not acceptable). Trials had to include adult patients with high-grade glioma who had undergone surgery and were then allocated radiotherapy plus chemotherapy or radiotherapy alone. The comparison had to be unconfounded by additional agents or interventions (ie, control and experimental groups had to differ only by addition of chemotherapy). The protocol specified that enrolment should have started after Jan 1, 1965, and have been completed by June 30, 1997. The later cut-off date was subsequently revised to include all closed trials at the time of the final data collation.

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.[10] 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

Ref	Accrual dates	Relevant treatment groups	Eligible histology	Eligible surgery	Delay*	Radiotherapy details	Chemotherapy details	n†
25‡	NK	All	Astrocytoma, grade III/IV	NK	2	Whole brain; 50 Gy; 25 fractions; 5 weeks: or 25 Gy; 10 fractions; 5 weeks, split course, 3 weeks rest then repeat; cobalt-60 or 4 MV linear accelerator	Dianhydrogalactitol 25 mg/m^2; ×5 intravenously; every 5 weeks for year 1 and 10 weeks thereafter	43
24	1970–72	2/3§	Astrocytoma grade III/IV	Resection, biopsy	2	Whole brain; 50 Gy; 25–28 fractions; every 30–39 days; cobalt-60 or 4 or 6 MV linear accelerator	Lomustine 130 mg/m^2 orally, every 8 weeks	41
20	1974–78	2/3§	Astrocytic glioma	Resection	4	Whole brain; 45 Gy; 25 fractions; 5 weeks; megavoltage	Bleomycin 15 mg intravenously×12 days 1 h before radiotherapy; control group received placebo	80
22	NK	All	Malignant glioma (not requiring steroids)	Optimum resection	3	55–60 Gy; 30 fractions; 6 weeks; betatron or telecobalt	Lomustine 130 mg/m^2 orally, every 6 weeks	111
22	NK	All	Malignant glioma (requiring steroids)	Optimum resection	3	55–60 Gy; 30 fractions; 6 weeks; betatron or telecobalt	Lomustine 130 mg/m^2 orally, every 6 weeks	23
23¶	NK	All	Astrocytoma grade III, glioblastoma multiforme	Partial resection	2	Whole brain; 50–60 Gy; 25–30 fractions; 5–6 weeks; cobalt-60 or megavoltage	Nimustine 100 mg/m^2, every 4–5 weeks, two courses	105
21‖	1979–82	All**	Astrocytoma, grade III/IV (WHO/Zulch)	Large resection	4	Whole brain; 40 Gy; 10 fractions; 5 weeks; or 50 Gy; 25 fractions; 5 weeks; megavoltage	Lomustine 120 mg/m^2 orally, every 6 weeks	280

NK=not known. *Maximum delay after surgery (weeks). †Number of patients randomised. ‡2×2 factorial design. §Remaining groups not relevant. ¶Envelope randomisation design. ‖2×2×2 factorial design. **Randomised using local lists.

Table 2: **Characteristics of unavailable eligible trials**

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[9] 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.[11] Thus, the times to event (progression or death) for individual patients were used within trials to calculate the hazard ratio, representing 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 for 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.[12] 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. χ^2 heterogeneity tests[13] were used to test for gross statistical heterogeneity across trials. χ^2 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.[14] All p values quoted are two-sided.

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 date of birth,[15,16] one allocated treatments by an alternating sequence,[17] and one was confounded by the use of hyperbaric oxygen in the control group only.[18] One trial[19] had several treatment groups that were operational at different times, with no concurrent randomisation to the treatment groups that were relevant to our meta-analysis. 19 trials were therefore available for inclusion. Seven trials that included a total of 683 patients were not available.[20–25] Data for two of these (SGSG1,[20] SGSG2[21]) were traced through the principal investigator to pharmaceutical companies that were unable to trace the trials and therefore unable to collaborate. Data from two other old trials (launched 1974) were lost through a failure in archive systems (EORTC 26741, EORTC 26742[22]). Data were not available for one trial,[23] and the institution responsible for the remaining two trials was

	Radiotherapy plus chemotherapy (n=1698)	Radiotherapy alone (n=1306)	Total
Age, years			
⩽40	291 (17%)	218 (17%)	509
41–59	914 (54%)	714 (55%)	1628
⩾60	474 (28%)	362 (27%)	836
Unknown	19 (1%)	12 (1%)	31
Sex			
Male	971 (57%)	776 (59%)	1747
Female	709 (42%)	518 (40%)	1227
Not recorded	18 (1%)	12 (1%)	30
Histology			
Anaplastic astrocytoma	400 (24%)	306 (24%)	706
Glioblastoma multiforme	1062 (62%)	838 (64%)	1900
Other	98 (6%)	80 (6%)	178
Unknown	138 (8%)	82 (6%)	220
Performance status*			
Good	634 (37%)	591 (45%)	1225
Poor	560 (33%)	438 (34%)	998
Unknown	504 (30%)	277 (21%)	781
Extent of resection			
Complete	432 (25%)	317 (24%)	749
Incomplete	953 (56%)	723 (55%)	1676
Biopsy	262 (16%)	231 (18%)	493
Unknown	51 (3%)	35 (3%)	86

*Three trials WHO/ECOG, six trials Karnofsky.

Table 3: **Characteristics of patients**

unable to collaborate.[24,25] No further relevant trials either completed or under way were identified by further searches done during 1999 and 2000.

The main results are therefore based on information from 12 randomised controlled trials[26–36] (and one unpublished trial by the EORTC Brain Group), which included 3004 patients—81% of individuals from all known, eligible randomised trials. Data were gathered for 210 of the 253 patients who had been excluded from the original published analyses and were reinstated in the meta-analysis.

For one trial,[27] 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,[34] 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.

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[31] 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 all trials, and data on performance status for nine trials, including the unpublished EORTC trial.[26–28,31–33,35,36] Grade data were available for only four trials[26,29,33,36] and so were insufficient for subgroup analyses. Data for cause of death (coded as glioma, treatment related, or other) were provided for eight trials[26,27,30,31,33,35,36] (and the unpublished trial), although the trialists themselves questioned the reliability of this information for many of the trials.

The average median follow-up was 2 years for surviving patients (8 months to 3 years 6 months for individual trials). The patients' characteristics, which reflect the eligibility criteria of individual trials, are given in table 3.

Survival analyses

Survival data were available for all 12 trials and included information on 3004 patients and 2659 deaths. Although the CIs for individual trial results were wide and the results of most inconclusive, all but one hazard ratio estimates were in favour of adjuvant chemotherapy

	Number of events/total			
Ref	RT+chemo	RT alone	O–E	Variance
26	91/100	87/93	−5·93	42·14
27	10/10	10/10	−2·02	4·41
28	210/238	104/117	−10·32	64·51
29	58/72	29/33	−3·91	17·09
30	310/344	152/167	−14·79	95·60
31	46/61	43/55	0·97	22·09
32	134/153	141/156	−12·31	67·24
33	57/59	32/32	−12·73	13·81
34	52/71	39/54	−1·10	21·25
Unpubl	93/120	102/115	−10·48	48·00
35	308/335	312/339	−8·72	153·67
36	115/135	124/135	−19·54	58·14
Total	1484/1698	1175/1306	−100·9	607·95

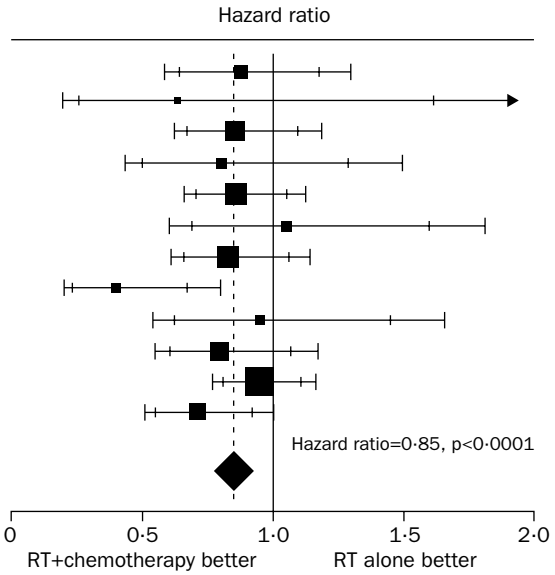
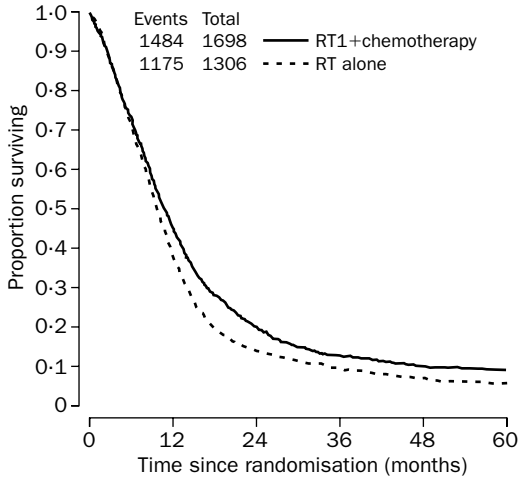


Figure 1: **Hazard ratio plot for survival**

χ^2=16·73, p<0·0001; heterogeneity χ^2=13·29, p=0·28. RT=radiotherapy; Chemo=chemotherapy. O–E=observed minus expected events. Each trial is represented by a square, the centre denoting the hazard ratio for that trial; extremities of horizontal bars denote 99% CI and inner bars 95% CI. The size of the square is directly proportional to amount of information in the trial. The black diamond at the foot of the plot gives the overall hazard ratio for combined results of all trials; the centre denotes the hazard ratio and extremities the 95% CI. Trials are ordered by date of start.



Patients at risk

RT+chemotherapy	1698	720	295	149	96	68
RT alone	1306	456	155	86	45	28

Figure 2: **Kaplan-Meier curve for survival**

(figure 1). There was no clear evidence of statistical heterogeneity (p=0·28) between trials. The combined results showed a significant increase in survival associated with the use of chemotherapy (p<0·0001). The hazard ratio of 0·85 (95% CI 0·78–0·92), representing a 15% relative reduction in the risk of death, is equivalent to an absolute improvement of 6% (3–9) at 1 year, increasing overall survival from 40% to 46%. At 2 years, the estimate is equivalent to a 5% (2–8) increase, from 15% to 20%. The advantage of chemotherapy is also shown in the survival curves (figure 2), which seemed to separate from around 6 months onwards.

A sensitivity analysis excluding one trial, for the reasons discussed above,[34] had little effect on the pooled result (hazard ratio 0·84 [0·78–0·92], p<0·0001). There was no difference in the results (interaction p=0·84) between trials that used single-agent chemotherapy (0·84 [0·75–0·93]) and those using combination chemotherapy (0·85 [0·76–0·94]). In a supplementary analysis, there was no clear evidence that the trials giving higher total doses of radiotherapy (60 Gy) showed substantially different results from those giving 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[35] 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

	Number of events/total			
Ref	RT+chemo	RT alone	O–E	Variance
27	10/10	10/10	−3·62	3·78
29	59/72	30/33	−6·46	16·96
30	316/344	153/167	−9·82	98·87
31	54/61	48/55	−1·00	25·14
33	57/59	32/32	−13·84	13·53
Unpubl	100/120	102/115	−12·21	49·25
35	318/335	320/339	−8·30	157·97
36	121/135	129/135	−25·69	58·34
Total	1035/1136	824/886	−80·69	423·83

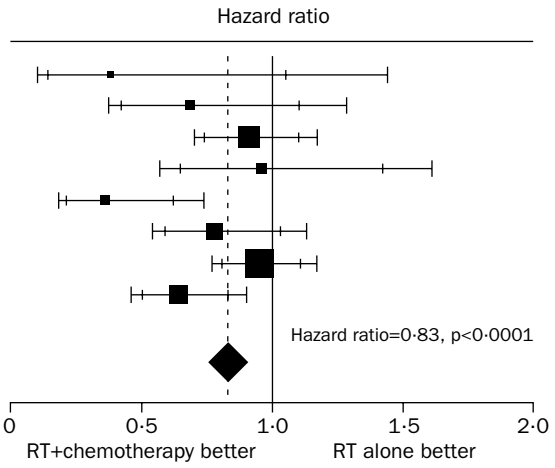


Figure 3: **Hazard ratio plot for progression-free survival**
χ^2=15·36, p<0·0001; heterogeneity χ^2=20·07, p=0·005.

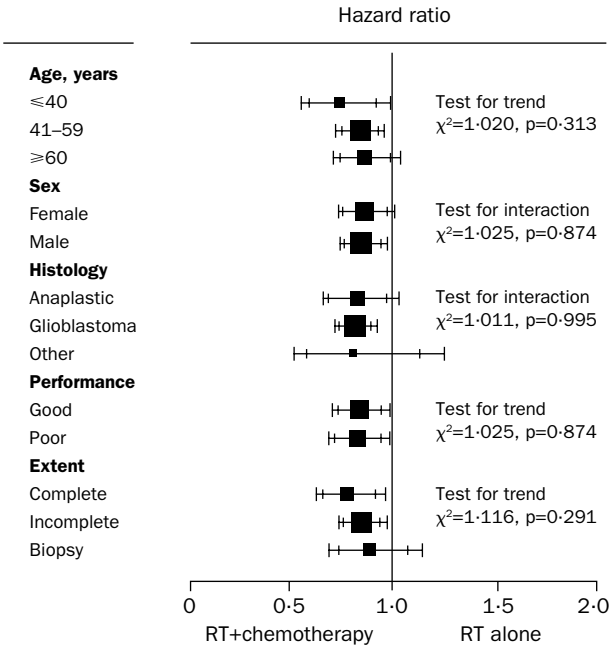


Figure 4: **Subgroup analyses**

average effect of chemotherapy in adults with high-grade glioma, to provide guidance for clinical practice and future research.

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 nitrosoureas, 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

Characteristic	1-year survival		2-year survival	
	Baseline (%)	Absolute increase (%)	Baseline (%)	Absolute increase (%)
Age, years				
≤40	78	3	50	5
41–59	45	6	14	5
≥60	22	6	4	2
Sex				
Male	45	6	18	5
Female	40	6	16	5
Histology				
Anaplastic astrocytoma	58	5	31	6
Glioblastoma multiforme	35	6	9	4
Other	72	4	52	5
Performance status				
Good	54	5	22	6
Poor	31	6	9	4
Extent of resection				
Complete	50	5	19	5
Incomplete	40	6	16	5
Biopsy	36	6	19	5

Table 4: **Baseline survival and respective absolute increases**

does show that high-grade gliomas can respond to chemotherapy and that further research into newer chemotherapies 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 Áfra, B Baron, G Bonadonna, W J Curran, S B Green, J Hildebrand, C B Scott, W Shapiro, D Thomas, T Trojanowski, R Urtasun, 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.

GMT Group

D Áfra (National Institute of Neurosurgery, Budapest, Hungary), B Baron (EORTC Data Center, Brussels, Belgium), G Bonadonna (Istituto Nazionale Tumori, Milan, Italy), S Burdett, M K B Parmar, S P Stenning, L A Stewart (MRC Clinical Trials Unit, London, UK), W J Curran Jr (Jefferson Medical College, Philadelphia, PA, USA), S B Green (Case Western Reserve University, Cleveland, OH, USA), J Hildebrand (Hopital Universitaire Erasme, Brussels, Belgium), C B Scott (Radiation Therapy Oncology Group, Philadelphia, PA, USA), W Shapiro (Barrow Neurological Institute, St Joseph's Hospital and Medical Center, Phoenix, AZ, USA), R L Souhami (Royal Free and University College Medical School, London, UK), D Thomas (National Hospital, London, UK), T Trojanowski (Medical School, Lublin, Poland), R C Urtasun (University of Alberta, Cross Cancer Institute, Edmonton, Alberta, Canada), M D Walker (National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA)

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.

References

1 Souhami R, Tobias J. Cancer and its management, second edn. Oxford: Blackwell Sciences: 1995.
2 Bleehen NM, Stenning SP. A Medical Research Council trial of two radiotherapy doses in the treatment of grades 3 and 4 astrocytoma. *Br J Cancer* 1991; **64:** 769–74.
3 Stenning SP, Freedman LS, Bleehen NM. An overview of published results from randomised studies of nitrosoureas in primary high-grade malignant glioma. *Br J Cancer* 1987; **56:** 89–90.
4 Fine HA, Dear KBG, Loeffler JS, Black PM, Canellos GP. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. *Cancer* 1993; **71:** 2585–97.
5 Schulz KF, Chalmers I, Hayes RJ, Altman DA. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995; **273:** 408–12.
6 Dickersin K. The existence of publication bias and risk factors for its occurrence. *JAMA* 1990; **263:** 1385–89.
7 Stewart LA, Parmar MKB. Meta-analysis of the literature or of individual patient data: is there a difference? *Lancet* 1993; **341:** 984.
8 Clarke M, Godwin J. Systematic reviews using individual patient data: a map for the minefields? *Ann Oncol* 1998; **9:** 827–33.
9 Stewart LA, Clarke MJ, on behalf of the Cochrane Working Party Group on Meta-analysis using Individual Patient Data. Practical methodology of meta-analyses (overviews) using updated individual patient data. *Stat Med* 1995; **14:** 2057–79.
10 Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994; **309:** 1286–91.
11 Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta-blockade during and after myocardial infarction: an overview of the randomised trials. *Prog Cardiovasc Dis* 1985; **27:** 335–71.
12 Parmar MKB; Machin D. Survival analysis: a practical approach. Chichester: John Wiley, 1995.
13 Early Breast Cancer Trialists Collaborative Group. Treatment of early breast cancer vol 1: worldwide evidence 1985–1990. Oxford: Oxford University Press, 1990.
14 Kaplan EL, Meier P. Non-parametric estimation from incomplete observation. *J Am Stat Assoc* 1958; **53:** 457–81.
15 Müller H, Brock M, Ernst H. Long-term survival and recurrence free interval in combined surgical, radio- and chemotherapy of malignancy brain gliomas. *Clin Neurol Neurosurg* 1985; **87:** 167–71.
16 Garrett MJ, Hughes HJ, Freedman LS. A comparison of radiotherapy alone with radiotherapy and CCNU in cerebral glioma. *Clin Oncol* 1978; **4:** 71–76.
17 Cianfriglia F, Pompili A, Riccio A, Grassi A. CCNU-chemotherapy of hemispheric supratentorial glioblastoma multiforme. *Cancer* 1980; **45:** 1289–99.
18 Brisman R, Housepian E, Chang C, Duffy P, Balis E. Adjuvant nitrosourea therapy for glioblastoma. *Arch Neurol* 1976; **33:** 745–50.
19 Ushio Y, Akagi K, Bitoh S, et al. Phase 3 study of methyl-CCNU and bleomycin combination chemotherapy in the treatment of malignant gliomas. Proceedings of the 7th International Congress of Neurological Surgery in Munich 1981: 362.
20 Kristiansen K, Hagen S, Kollevold T, et al. Combined modality therapy of operated astrocytomas grade III and IV: confirmation of the value of postoperative irradiation and lack of potentiation of bleomycin on survival time. *Cancer* 1981; **47:** 649–52.
21 Hatlevoll R, Lindegaard K, Hagen S, et al. Combined modality treatment of operated astrocytomas grade 3 and 4: a prospective and randomised study of misonidazole and radiotherapy with two different radiation schedules and subsequent CCNU chemotherapy. *Cancer* 1985; **56:** 41–47.
22 EORTC Brain Tumor Group. Effect of CCNU on survival rate of objective remission and duration of free interval in patients with malignant brain glioma: final evaluation. *Eur J Cancer* 1978; **14:** 851–56.
23 Takakura K, Abe H, Tanaka R, et al. Effects of ACNU and radiotherapy on malignant glioma. *J Neurosurg* 1986; **64:** 53–57.
24 Reagan TJ, Bisel HF, Childs DS, Layton DD, Rhoton AL, Taylor WF. Controlled study of CCNU and radiation therapy in malignant astrocytoma. *J Neurosurg* 1976; **44:** 186–90.
25 Eagan RT, Childs DS, Layton DD, et al. Dianhydrogalactitol and radiation therapy: treatment of supratentorial glioma. *JAMA* 1979; **241:** 2046–50.
26 Walker MD, Alexander E Jr, Hunt WE, et al. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. *J Neurosurg* 1978; **49:** 333–43.
27 Weir B, Band P, Urtasun R, et al. Radiotherapy and CCNU in the treatment of high-grade supratentorial astrocytomas. *J Neurosurg* 1976; **45:** 129–34.
28 Walker MD, Green SB, Byar DP, et al. Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. *N Engl J Med* 1980; **303:** 1323–29.
29 Solero CL, Monfardini S, Brambilla C, et al. Controlled study with BCNU versus CCNU as adjuvant chemotherapy following surgery plus radiotherapy for glioblastoma multiforme. *Cancer Clin Trials* 1979; **2:** 43–48.
30 Chang CH, Horton J, Schoenfeld D, et al. Comparison of postoperative radiotherapy and combined postoperative radiotherapy and chemotherapy in the multidisciplinary management of malignant gliomas. *Cancer* 1983; **52:** 997–1007.
31 EORTC Brain Tumor Group. Evaluation of CCNU, VM-26 plus CCNU and procarbazine in supratentorial brain gliomas. *J Neurosurg* 1981; **55:** 27–31.

32 Green SB, Byar DP, Walker MD, et al. Comparisons of carmustine, procarbazine and high-dose methylprednisolone as additions to surgery and radiotherapy for the treatment of malignant glioma. *Cancer Treat Rep* 1983; **67:** 121–32.
33 Áfra D, Kocsis B, Dobay J, Eckhardt S. Combined radiotherapy and chemotherapy with dibromoducitol and CCNU in the postoperative treatment of malignant gliomas. *J Neurosurg* 1983; **59:** 106–10.
34 Trojanowski T, Peszynski J, Turowski K, et al. Post-operative radiotherapy and radiotherapy combined with CCNU chemotherapy for treatment of brain gliomas. *J Neuro-Oncol* 1988; **6:** 285–91.
35 Medical Research Council Brain Tumour Working Party. A randomised trial of adjuvant chemotherapy in malignant glioma. *J Clin Oncol* 2001; **19:** 509–18.
36 Hildebrand J, Sahmoud T, Mignolet F, Brucher JM, Áfra D. Adjuvant therapy with dibromoducitol and BCNU increases survival of adults with malignant gliomas. *Neurology* 1994; **44:** 1479–83.