Chemotherapy for high-grade glioma (Review)

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[Intervention Review]

Chemotherapy for high-grade glioma

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ABSTRACT

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.

Objectives

To compare radiotherapy plus chemotherapy with radiotherapy alone in completely resected adults with high-grade glioma. To investigate whether or not pre-defined patient subgroups benefit more or less from chemotherapy.

Search methods

MEDLINE and CancerLit searches were supplemented with information from trial registers and by hand searching relevant meeting proceedings and by discussion with relevant trialists and organisations. These searches were carried out in June 1997, June 1999, December 2000 and August 2003.

Selection criteria

Trials comparing radiotherapy versus radiotherapy + chemotherapy were eligible for inclusion provided that they randomized adult patients using a method which precluded prior knowledge of treatment assignment.

Data collection and analysis

A quantitative meta-analysis using updated information from individual patients from all available randomized trials was carried out. Data from all patients randomized in all eligible trials were sought directly from those responsible. Updated information on survival and date of follow-up were obtained, as were details of treatment allocation, date of randomization, age, sex, histological cell type, stage and performance status. To avoid potential bias, information was requested for all randomized patients including those who had been excluded from the investigators' original analyses. All analyses were done on an intention to treat basis on the endpoint of survival. For trials using cisplatin-based regimens, subgroup analyses by age, sex, histological cell type, tumour stage and performance status were also done.

Main results

Data from 12 randomized trials and 3004 patients were included. The results show a significant prolongation of survival associated with chemotherapy, with a hazard ratio of 0.85 (95% CI 0.78-0.91, p=0.00004) or 15% relative decrease in the risk of death. This is equivalent to an absolute increase in one year survival rate of 6% (95% confidence interval 3% to 9%) from 40% to 46% and a two-month increase in median survival time (95% confidence interval one month to three months). There was no evidence that the effect of chemotherapy was different in any group of patients defined by age, sex, histology, performance status or extent of resection.

Authors' conclusions

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

PLAIN LANGUAGE SUMMARY

Including chemotherapy in the treatment of high-grade glioma improves survival

High-grade glioma is a brain tumour that is difficult to treat successfully. Standard treatment is by surgery to reduce the tumour size, followed by radiotherapy. Adding chemotherapy to the treatment results in a small but significant prolongation of survival. Few of the original studies measured quality of life during and post chemotherapy, so it was impossible to assess this. Further randomized controlled trials, which include quality of life assessment, are encouraged.

BACKGROUND

Malignant gliomas are amongst the most devastating of cancers, frequently producing profound and progressive disability and usually leading to death. They are difficult to diagnose and challenging to treat. Incidence peaks in children and at 50 to 60 years of age (Souhami 1995). These tumours are therefore a major cause of mortality in a relatively young population and improving 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, and even if possible it may 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 nine months and only five to ten per cent of patients surviving to two years (Bleehen 1991). Consequently, a number of randomized trials have explored the use of adjuvant chemotherapy, with research mostly focusing on the use of nitrosoureas which are used because they are lipid soluble and cross the blood-brain barrier. The majority of these trials, which have been carried out over a period of almost thirty years, have been relatively small, and many have randomized between multiple treatment arms. It is not surprising then, that most have shown inconclusive results and that there is consequently no consensus on the value of chemotherapy treatment

Combining the results of trials in a meta-analysis increases statistical power and may provide sufficient information to answer the question of survival benefit more reliably. Two meta-analyses based on summary data extracted from trial reports have been published (Stenning 1987; Fine 1993). However, these suffer from a number of limitations and potential biases. Each identified only a proportion of currently relevant trials and included trials that used pseudo-random methods of allocation which are known to be liable to bias (Schulz 1995). They were limited to published trials, thereby susceptible to publication bias (Dickersin 1990), and many of the trials excluded considerable numbers of patients (on average 10-15%) from their published analyses potentially introducing further bias. Importantly, there is strong evidence from the cancer field that meta-analyses based on data extracted from published reports can give different results from those based on updated individual patient data (Stewart 1993; Clarke 1995) We therefore initiated a systematic review and individual patient data (IPD) meta-analysis to collect, validate and re-analyse trial data on all randomized patients from all relevant trials. There are many advantages of collecting IPD in a meta-analysis such as this (Stewart 1995). In particular, it permits time-to-event analyses which, in a disease such a malignant glioma where prolongation of survival rather than cure is anticipated, is extremely important. It also allows us to conduct analyses to assess whether chemotherapy may be more or less effective in different subgroups of patients. The IPD meta-analysis was initiated and coordinated by the British Medical Research Council Clinical Trials Unit and carried out by the Glioma Meta-analysis Trialists (GMT) group.

OBJECTIVES

To compare radiotherapy plus chemotherapy with radiotherapy alone in completely resected adults with high-grade glioma. To investigate whether or not pre-defined patient subgroups benefit more or less from chemotherapy.

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METHODS

Criteria for considering studies for this review

Types of studies

Both published and unpublished trials were eligible for inclusion. Trials should have been properly randomized in a way which precluded prior knowledge of treatment assignment (trials which allocated treatment by pseudo-random methods such as birthdate were excluded). Trials should have aimed to randomize patients with high-grade glioma, who had undergone surgery and were then allocated radiotherapy and chemotherapy or radiotherapy alone. Recruitment should have started after January 1st 1965 and completed by June 30th 1997.

Types of participants

Eligible trials included individuals with high-grade glioma who have not received any prior treatment for any other malignancy likely to interfere with protocol treatments or comparisons. Individual data from all randomized patients were included in the meta-analysis and where possible data were obtained for individuals who had been excluded from the original trial analyses. These individuals were included in the meta-analysis.

Types of interventions

Surgery + radiotherapy + chemotherapy versus surgery + radiotherapy
Details of surgery, radiotherapy and chemotherapy are given in Characteristics of Included Studies

Types of outcome measures

Survival
Recurrence-free survival

Search methods for identification of studies

To avoid publication bias, both published and unpublished trials were included. Computerised bibliographic searches of MEDLINE and CancerLit were made (06/1997, 06/1999, 12/2000) using a version of the Cochrane Collaboration optimal search strategy (Dickersin 1994). Searches were not limited to trials reported in English language journals. This strategy was also modified and used to search Embase. These electronic searches were supplemented by hand searching the reference lists of identified trials, and bibliographies of relevant books and review articles. The National Cancer Institute Physicians Data Query (PDQ) Clinical Protocols and the United Kingdom Coordinating Committee for Cancer Research Trials Register were also searched to identify both completed and ongoing trials. All trialists who took part in the meta-analysis were asked to help to identify trials. 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 obtained for all abstracts judged potentially relevant. Where there was uncertainty about the eligibility of a trial, or particular treatment arms within a trial, this was discussed and resolved by consensus within the project secretariat, and ratified by the GMT group at a meeting held in July 1999.
1 Randomized-Controlled-Trial.pt.
2 Randomized Controlled Trials/
3 Random Allocation/
4 Double-Blind Method/
5 Single-Blind Method/
6 1 or 2 or 3 or 4 or 5
7 Animal.DE.
8 Human.DE.
9 7 NOT (7 AND 8)
10 6 NOT 9
11 Clinical-Trial.pt.
12 Clinical-Trials/
13 (Clin$ WITH Trial$).ab,ti.
14 ((Sing$ OR Doub$ OR Trebl$ OR Tripl$) ADJ (Blind$ OR MaskS)).ab,ti.
15 Placebo$.ab,ti.
16 Random.ab,ti.
17 Research Design/
18 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
19 18 NOT 9
20 19 NOT 10
21 10 NOT 20
22 Brain-Neoplasms.DE.
23 Drug-Therapy.DE.
24 22 AND 23
25 21 AND 24
26 Brain ADJ Neoplasm$
27 Glioma$
28 26 OR 27
29 Chemotherapy

30 28 AND 29
31 25 OR 30
32 Child#.DE.
33 31 NOT 32

Data collection and analysis

This review is based on individual patient data obtained directly from the responsible trialist or data centre. It does not use information extracted from published papers. All data were collected, checked and analysed centrally.

Data were sought for all patients randomized in all eligible randomized trials (published or unpublished) and updated follow-up requested. For all comparisons the following data were collected: patient identifier, treatment allocated, date of randomization, survival status, date of last follow-up or death and whether the individual was excluded from the original analyses. Data on age, sex, stage, histology and performance status were also collected. Collection and validation of data were carried out at the MRC Cancer Trials Office (now the Cancer Division of the MRC Clinical Trials Unit).

All data were checked thoroughly and a common database was agreed. The final database entries for each trial were verified by the responsible trialist or data centre.

For trials with multiple treatment arms the eligibility of each individual arm was assessed and only the relevant arms were included. Characterisitics of Included Studies provides further information on this.

All analyses were carried out on an intention-to-treat basis, that is, patients were analysed according to their allocated treatment, irrespective of whether they received that treatment. Survival analyses were stratified by trial, and the log rank expected number of deaths and variance used to calculate individual trials and overall pooled hazard ratios (HR) using the fixed effect model (Yusuf 1985). Thus, the times to event (progression or death) for individual patients were used within trials to calculate the HR, representing the overall risk of an event for those patients allocated to adjuvant chemotherapy compared with those allocated to no chemotherapy. To investigate the effects of chemotherapy within subgroups of patients, similar stratified analyses were done. Analyses were performed for each pre-specified category, for example, comparing treatment and control for males and for females within each individual trial. These results were then combined to give overall HRs for males and for females. Results are also presented as absolute differences at one and two years, calculated using the overall HRs and event rate on the control (Parmar 1995). Absolute effects for different types of patients defined by categories used in our sub-group analyses were calculated using the overall HR and event rates on the surgery alone arm for each subgroup. Confidence intervals for absolute differences were calculated from the baseline event rate and the HR at the 95% confidence interval boundary values. Chi-square heterogeneity tests (EBCTCG 1990) were used to test for gross statistical heterogeneity across trials. Survival curves are presented as simple (non-stratified) Kaplan-Meier curves (Kaplan 1958) . All p-values quoted are two-sided.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

In total, 24 trials were identified as potentially eligible for the meta-analysis. Five of these were found to be ineligible and therefore excluded. The reasons for exclusion are listed in the table of excluded studies. Of the 19 eligible trials, data were not available from seven trials as they had been lost, destroyed or were untraceable. These trials are also listed in the table of excluded trials. Data from 12 randomized trials and 3004 patients are therefore included in this meta-analysis. This represents 81% of individuals from all known eligible randomized trials. Data were collected 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 (Alberta) we were unable to obtain information from eight patients. As the missing patients were few and distributed evenly across treatment arms the trial was included. In another trial, (Poland) data had to be read from archived computer printouts and we were unable to retrieve information on 19 patients that had become detached from the end of the listing. As these missing patients were not evenly distributed on treatment arms, the main analyses were done both with and without this trial. Design features of all eligible trials are shown in Characteristics of Included Studies. Of the included trials, total radiotherapy doses ranged from 40 Gy to 60 Gy given in between 25 and 35 fractions. Four trials delivered whole brain irradiation whilst eight irradiated the tumour plus margins. The maximum planned delay between surgery and radiotherapy/chemotherapy ranged from two to six weeks and all but one trial (EORTC 26741) randomized prior to radiotherapy. All trials included at least one nitrosourea compound, given either as a single agent or in combination with other drugs. Chemotherapy regimens and planned drug doses are given in Characteristics of Included Studies. Although trials were able to provide most of the baseline patient characteristic data 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. Grade data were available for only four trials and so were insufficient for subgroup analyses. Cause of death data (coded as glioma, treatment related and other) were provided for eight trials although the trialists themselves questioned the reliability of this information for many of the trials. The average median follow up is two years for surviving

patients (eight months to three years six months for individual trials). The patient characteristics which reflect the eligibility criteria of individual trials are given in Table 1. Patients were mostly male, fairly young with glioblastoma multiforme and had received an incomplete resection.

Risk of bias in included studies

Only trials with adequate methods of randomization (those which did not allow prior knowledge of treatment assignment) were included. All data received were checked thoroughly to ensure both the accuracy of the meta-analysis database and the quality of randomization and follow up. Any queries were resolved and the final database entries verified by the responsible trial investigator or statistician.

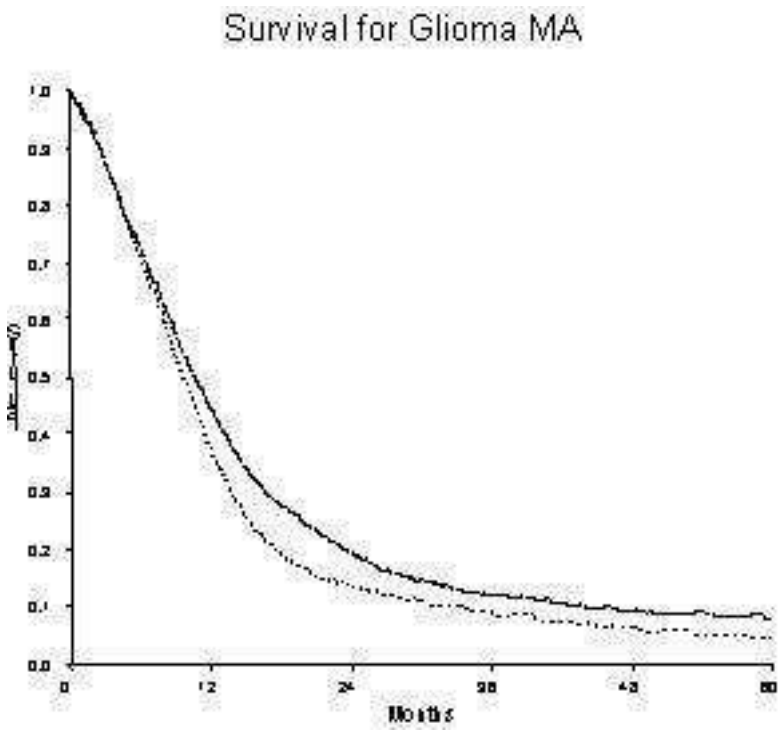
Effects of interventions

Survival data were available for all 12 trials and included information on 3004 patients and 2659 deaths. Although the confidence intervals for individual trial results are wide and the results of most inconclusive, all but one HR estimate is in favour of adjuvant chemotherapy (Outcome 01: Survival). There is no clear evidence of statistical heterogeneity (p=0.275) between trials. The combined results show a statistically significant increase in survival (p=0.00004) associated with the use of chemotherapy. 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% at one year (95% CI 3% to 9%) increasing overall survival from 40% to 46%. At two years it is equivalent to a five per cent (95%CI 2% to 8%) increase from 15% to 20%. This advantage of chemotherapy is also illustrated in the survival curves, which are presented in the meta-analysis publication (GMT Group), which appear to separate at around six months and then remain apart over time. A sensitivity analysis excluding one trial (Poland) for the reasons discussed above had minimal impact on the pooled result (HR=0.84, 95% CI 0.78-0.92, p= 0.00003). There was no difference in the results (interaction p= 0.84) between trials using single-agent chemotherapy (HR=0.84, 95% CI 0.75-0.93) and those using combination chemotherapy (HR=0.85, 95%CI 0.76-0.94). In a supplementary analysis, there was no clear evidence that those trials giving higher total doses of radiotherapy (>=60Gy) showed substantially different results to those using lower radiotherapy doses (<60Gy), with HRs of 0.88 and 0.77 (95%CI) respectively, (interaction p=0.11). A further analysis excluding the individual trial (MRC BR05) that had suggested an interaction between radiotherapy dose and effect of chemotherapy also showed no evidence that results of trials using lower radiotherapy doses of >=60Gy were any different to those using doses of <60Gy (interaction p= 0.68) with HRs of 0.83 and 0.79 respectively. A sensitivity analysis based on only those patients with glioblastoma multiforme and anaplastic astrocytoma gave a very similar estimate to the main result (HR=0.83, 95%CI 0.76-0.90, p=0.000013).

Progression-Free Survival

Information on disease progression was available from eight trials and a total of 2022 patients. A total of 1859 events were observed. Results show a similar pattern to survival. The overall HR of 0.83 (95% CI = 0.75 - 0.91) (Figure 1), indicates a statistically significant (p=0.00008) 17% reduction in the risk of progression or death, This is equivalent to an absolute benefit of five per cent at two years (95% confidence interval 2 to 8%) increasing progression-free survival from 10% to 15%. Median progression-free survival is increased by one and a half months (95% CI 0.5 to 2.5 months) from six months to seven and a half months.

Figure 1. Events Total
RT + Chemo ____ 1484 1698
RT alone ---------- 1175 1306Patients at risk
RT + Chemo - 1698 - 720 (1 yr), 295 (2 yrs), 149 (3 yrs), 96 (4 yrs), 68 (5yrs)
RT alone - 1306 - 456 (1 yr), 155 (2 yrs), 86 (3 yrs), 45 (4 yrs), 28 (5 yrs)



Subsidiary Analyses in Patient Subgroups

Analyses were performed to determine whether there was evidence of a differential effect of chemotherapy in pre-defined subgroups of patients. For survival there was no evidence to suggest that chemotherapy was differentially effective in any group of patients defined by age (trend p=0.313), sex (interaction p=0.874), histology (interaction, p=0.995), performance status (interaction p=0.872) or extent of resection (trend p=0.291) (Outcomes 03-07).

Analysis of published data for unavailable trials

Because information was not available from seven trials accounting for 683 patients, an analysis based on data extracted from publications was done for the six trials (EORTC 26741; EORTC 26742; Hatlevoll 1985; Eagan 1979; Reagan 1976; Kristiansen 1981) for which appropriate data could be extracted. This used numbers of patients who had died by two years to calculate an odds ratio (OR). This analysis gave results that were broadly similar to the results of our IPD analysis. (OR = 0.92, 95%CI 0.79 - 1.09).

DISCUSSION

At the outset of this project, despite the enrolment of more than 3500 patients in randomized trials, it remained unclear whether or not chemotherapy was effective in the treatment of high-grade glioma. Current clinical practice varies both 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 average effect of chemotherapy in adult patients with high-grade glioma, to provide guidance for clinical practice and future research.

For the primary endpoint of survival, there is clear evidence of a beneficial effect of adjuvant chemotherapy. The 15% relative reduction in the risk of death associated with chemotherapy is equivalent to an overall increase in survival from 40% to 46% at one year, to an increase from 10% to 15% at two years, and to a two month increase in median survival time from 10 to 12 months. Although many trials were completed some years ago and did not undergo central pathology review, there is no indication that these results are being driven by inclusion of chemo-sensitive

tumours e.g. oligodendrogliomas. A sensitivity analysis based on only the anaplastic astrocytoma and glioblastoma multiforme tumours gave results that were very close to the main result. In addition, the results of subgroup analyses illustrate a benefit of chemotherapy irrespective of histology and are 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 varies in the different patient subgroups included in the meta-analysis. Thus, the best estimate for any individual patient is that they are likely to gain around 15% reduction in the overall risk of death. However, given that the underlying prognoses for different categories of patients vary considerably, these relative effects are likely to translate to different absolute improvements in outcome rates. Baseline survival rates and corresponding absolute increases are shown in Table 2. This shows, for example, that the two-year survival rate for individuals with glioblastoma multiforme is increased from nine per cent to 13%, whereas for those with anaplastic astrocytoma it is increased from 31% to 37%.

As data were not available from around 19% of the total randomized evidence, we conducted a comparative analysis based on data presented in publications for the missing trials. Although there are many potential problems and biases with this approach, it is useful to compare how results from the unavailable trials compare to those included in the IPD analysis. In particular, it allows us to explore whether there is any obvious bias associated with trial availability, for example, did we only have access to the positive trials? The results of this analysis of survival at two years showed broadly similar results to our IPD analysis and apparent efficacy of chemotherapy. Thus we can be reasonably confident that, had we successfully obtained the missing data, it would not have substantially altered the results of our IPD analysis.

Undoubtedly, there are design differences in the trials included in the meta-analysis, particularly with respect to the radiotherapy regimens and techniques used. It could be suggested 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 HR 0.88 for just those trials delivering a total dose of 60Gy or more is not significantly different to that of the remainder of trials and very similar to the overall HR. Thus the effect of chemotherapy is apparent in those 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.

Although this meta-analysis has shown a clear benefit of chemotherapy of around six per cent at two years, and an improvement in median survival time of two months (from 10 to 12 months), whether this is of benefit clinically remains open to interpretation. This is, of course, likely to vary depending upon the clinical situation and individual patient and family preference. Clearly, tolerability of treatment and quality of life, including cognitive impairment, are major issues in judging this for patients who will usually survive only a short time after their treatment has finished. Few of the 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 the quality of the demonstrated prolongation of survival. However, when making decisions about treatment, the interpretation of such information is likely to be influenced by a myriad of personal beliefs and preferences, so that interpretation of these data in isolation may not be particularly helpful. In this respect the nitrosoureas, whilst not a novel method of treatment, are fairly well tolerated, easily administered, may be of practical use in the clinic for those individuals to whom it is important to extend their likely survival time, if only by a modest amount. Importantly, the clear effect observed in this comprehensive review, does demonstrate 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 concerning quality of life, is such that some clinical trialists would consider radiotherapy alone to be a justified standard therapy arm, whereas others may feel that the appropriate standard therapy arm should now include a nitrosourea. The small but clear improvement in survival from chemotherapy encourages further study of drug treatment of these tumours.

AUTHORS' CONCLUSIONS

Implications for practice

Although this meta-analysis has shown a clear benefit of chemotherapy of around six per cent at two years, and an improvement in median survival time of two months (from 10 to 12 months), whether this is of benefit clinically remains open to interpretation

Implications for research

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

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Contributors

All aspects of the meta-analysis were carried out under the auspices of the GMT Group.

D Áfra, B Baron, G Bonadonna, WJ Curran Jr, SB Green, J Hildebrand, CB Scott, W Shapiro, D Thomas, T Trojanowski, R Urtasun and MD Walker collated and supplied the individual patient data, contributed to the discussions of the results and commented on the drafts of the reports. The project was organised by the secretariat, S Burdett, MKB Parmar, RL Souhami, SP Stenning and LA Stewart, who were responsible for formulating the question, developing the protocol, receiving, checking and analysing the data.

The Project was managed by S Burdett.

The report was drafted by LA Stewart and S Burdett with detailed input from RL Souhami and SP Stenning.

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za Age - <=40 *{published and unpublished data}*

zb Age - 41-59 *{published and unpublished data}*

zc Age - >=60 *{published and unpublished data}*

zd Sex - Female *{published and unpublished data}*

ze Sex - Male *{published and unpublished data}*

zf Histology - AA *{published and unpublished data}*

zg Histology - GBM *{published data only}*

zh Histology - Other *{published and unpublished data}*

zi P Status - Good *{published and unpublished data}*

zj P Status - Poor *{published and unpublished data}*

zk Rsection-Complete *{published and unpublished data}*

zl Rsection- Incompl *{published and unpublished data}*

zm Rsection - Biopsy *{published and unpublished data}*

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alberta

Methods	RCT
Participants	28 -High grade astrocytoma -Resection biopsy
Interventions	CT + RT vs RT -CCNU 130mg/m2 oral q 6 wks -RT 40-45 Gy 25f 4-5 wks
Outcomes	Survival Recurrence-free survival
Notes	1971-1973 2 of 3 arms

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

BTSG 6901

Methods	RCT
Participants	193 -Anaplastic astrocytoma -Definitive surgical resection
Interventions	CT + RT vs RT -BNCU 80 mg/m2 x3 iv q 6-8 wks -RT 50-60 Gy 30-35f 6-7 wks
Outcomes	Survival
Notes	1969-1972 2 of 4 arms

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

BTSG 7201

Methods	RCT
Participants	356 -Malignant glioma -Definitive surgery
Interventions	CT + RT vs RT -MeCCNU 220mg/m2 oral q 6-8 wks -BCNU 80 mg/m2 x3 iv q 6-8 wks -RT 60 Gy 30-35f 6-7 wks
Outcomes	Survival
Notes	1972-1975 3 of 4 arms

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

BTSG 7501

Methods	RCT
Participants	309 -Malignant glioma -Definitive surgery
Interventions	CT + RT vs RT -BCNU 80mg/m2 x3 iv q 8 wks -PCZ 150mg/m2 x 28days q 8wks
Outcomes	Survival
Notes	1974-1978 2 of 4 arms

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Budapest

Methods	RCT
Participants	91 -Glioblastoma malignant astrocytoma grade III (WHO zulch) -At least sub-total resection
Interventions	CT + RT vs RT -DBD 400 mg/m2 q 5 days during RT month rest then repeat -DBD 400 mg/m2 q 5 days during RT 5-6 wks rest then CCNU 200 mg/m2 x5 q 4-6 wks -RT 51 Gy 25-30f 5-6 wks
Outcomes	Survival Recurrence-free survival
Notes	1978-1981

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

EORTC 26751

Methods	RCT
Participants	116 -Malignant glioma -Optimal resection
Interventions	CT + RT vs RT -CCNU 130mg/m2 oral % VM-26 60mg/m2 iv q 6 wks
Outcomes	Survival Recurrence-free survival
Notes	1975-1978 1st random

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

EORTC 26812

Methods	RCT
Participants	335 -Malignant: astrocytoma, glioblastoma, ependymoblastoma, oligodendroglioma
Interventions	CT + RT vs RT -CCNU 130 mg/m2 oral + VM-26 100mg/m2 IV q 6 wks
Outcomes	Survival Recurrence-free survival
Notes	1982-1987

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

EORTC 26882

Methods	RCT
Participants	270 -Anaplastic astrocytoma, glioblastoma -Resection stereotactic biopsy
Interventions	CT + RT vs RT -DBD 700 mg/m2 x7 oral during RT then BCNU 150 mg/m2 iv DBD 1000 mg/m2 oral q 6 wks
Outcomes	Survival Recurrence-free survival
Notes	1989-1991

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Milan

Methods	RCT
Participants	105 -Glioblastoma multiforme -Total or subtotal resection
Interventions	CT + RT vs RT -BCNU 80mg/m2 x3 iv q 6-8 wks -CCNU 130mg/m2 oral q 6-8 wks
Outcomes	Survival Recurrence-free survival
Notes	1972-1973 2 of 3 arms

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

MRC BR05

Methods	RCT
Participants	674 -Astrocytoma grade III/IV (WHO/Zulch)
Interventions	CT + RT vs RT -CCNU 100mg/m2 PCZ 100mg/m2 oral x 10 VCR 1.5mg/m2 q 6 wks
Outcomes	Survival Recurrence-free survival
Notes	1986-1997

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Poland

Methods	RCT
Participants	149 -Glioma, high and low grade
Interventions	CT + RT vs RT -CCNU 100mg/m2 oral q 6-8 wks
Outcomes	Survival
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

RTOG 7401

Methods	RCT
Participants	512 -Astrocytoma grade III/IV (Kernohan)
Interventions	CT + RT vs RT -BCNU 80mg/m2 x3 iv q 6-8 wks -MeCCNU 125mg/m2 oral q 8 wks DTIC 150mg/m2 x5 iv q 4 wks (doses initially 150mg/m2 & 175mg/m2 but reduced owing to severe toxicity)
Outcomes	Survival Recurrence-free survival
Notes	1974-1979 3 of 4 arms (institutions chose to randomise to 2 or 3 of the 4 arms. RTOG indicate that all institutes randomised between RT vs RT + chemo)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

za Age - <=40

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

zb Age - 41-59

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

zc Age - >=60

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

zc Age - >=60 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

zd Sex - Female

Methods
Participants
Interventions
Outcomes
Notes

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

ze Sex - Male

Methods
Participants
Interventions
Outcomes
Notes

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

zf Histology - AA

Methods
Participants
Interventions

zf Histology - AA (*Continued*)

Outcomes		
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

zg Histology - GBM

Methods		
Participants		
Interventions		
Outcomes		
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

zh Histology - Other

Methods		
Participants		
Interventions		
Outcomes		
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

zi P Status - Good

Methods		
Participants		
Interventions		
Outcomes		
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

zj P Status - Poor

Methods		
Participants		
Interventions		
Outcomes		
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

zk Rsection-Complete

Methods		
Participants		
Interventions		
Outcomes		
Notes		
Risk of bias		

zk Rsection-Complete (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

zl Rsection- Incompl

Methods
Participants
Interventions
Outcomes
Notes

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

zm Rsection - Biopsy

Methods
Participants
Interventions
Outcomes
Notes

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

CT=chemotherapy, RT=radiotherapy, f=fractions, q=every
Za-Zm are sub-group categories not trials

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Brisman 1976	Confounded by use of hyperbaric oxygen on control arm
Cianfriglia 1980	alternate allocation
Eagan 1979	Eligible but data unavailable
EORTC 26741	Eligible but data lost by data centre
EORTC 26742	Eligible but data lost by data centre
Garrett 1978	'randomized' by date of birth
Hatlevoll 1985	Eligible but data unavailable
Kristiansen 1981	Eligible but data unavailable
Muller 1985	'randomized' by date of birth
Reagan 1976	Eligible but data unavailable
Takakura 1986	Eligible but unable to participate
Ushio 1981	Several treatment groups operational at different times

DATA AND ANALYSES

Comparison 1. RT + Chemo vs RT alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival	12	3004	Peto Odds Ratio (99% CI)	0.85 [0.78, 0.92]
2 Progression-free Survival	8	2022	Peto Odds Ratio (99% CI)	0.83 [0.75, 0.91]
3 Survival subgroup analysis - age	3	2972	Peto Odds Ratio (99% CI)	0.83 [0.76, 0.90]
4 Survival subgroup analysis - sex	2	2659	Peto Odds Ratio (99% CI)	0.83 [0.76, 0.90]
5 Survival subgroup analysis - histology	3	2501	Peto Odds Ratio (99% CI)	0.79 [0.73, 0.87]
6 Survival subgroup analysis - performance status	2	2520	Peto Odds Ratio (99% CI)	0.82 [0.75, 0.89]
7 Survival subgroup analysis - extent of resection	3	2631	Peto Odds Ratio (99% CI)	0.82 [0.75, 0.89]

Analysis 1.1. Comparison 1 RT + Chemo vs RT alone, Outcome 1 Survival.

Review: Chemotherapy for high-grade glioma

Comparison: 1 RT + Chemo vs RT alone

Outcome: 1 Survival

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,99% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,99% CI
BTSG 6901	91/100	87/93		6.9 %	0.87 [0.58, 1.29]
Alberta	10/10	10/10		0.7 %	0.63 [0.19, 2.16]
BTSG 7201	210/238	104/117		10.6 %	0.85 [0.62, 1.17]
Milan	58/72	29/33		2.8 %	0.80 [0.43, 1.48]
RTOG 7401	310/344	152/167		15.7 %	0.86 [0.66, 1.11]
EORTC 26751	46/61	43/55		3.6 %	1.04 [0.60, 1.81]
BTSG 7501	134/153	141/156		11.1 %	0.83 [0.61, 1.14]
Budapest	57/59	32/32		2.3 %	0.40 [0.20, 0.80]
Poland	52/71	39/54		3.5 %	0.95 [0.54, 1.66]

(*Continued* . . .)

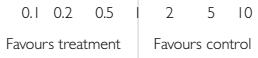
(. . . *Continued*)

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,99% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,99% CI
EORTC 26812	93/120	102/115		7.9 %	0.80 [0.55, 1.17]
MRC BR05	308/335	312/339		25.3 %	0.94 [0.77, 1.16]
EORTC 26882	115/135	124/135		9.6 %	0.71 [0.51, 1.00]
Total (95% CI)				**100.0 %**	**0.85 [0.78, 0.92]**

Heterogeneity: Chi² = 13.29, df = 11 (P = 0.27); I² =17%

Test for overall effect: Z = 4.09 (P = 0.000043)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 RT + Chemo vs RT alone, Outcome 2 Progression-free Survival.

Review: Chemotherapy for high-grade glioma

Comparison: 1 RT + Chemo vs RT alone

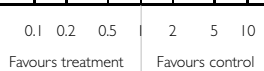
Outcome: 2 Progression-free Survival

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,99% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,99% CI
Alberta	10/10	10/10		0.9 %	0.38 [0.10, 1.44]
Milan	59/72	30/33		4.0 %	0.68 [0.36, 1.27]
RTOG 7401	316/344	153/167		23.3 %	0.91 [0.70, 1.17]
EORTC 26751	54/61	48/55		5.9 %	0.96 [0.57, 1.61]
Budapest	57/59	32/32		3.2 %	0.36 [0.18, 0.74]
EORTC 26812	100/120	102/115		11.6 %	0.78 [0.54, 1.13]
MRC BR05	318/335	320/339		37.3 %	0.95 [0.77, 1.16]
EORTC 26882	121/135	129/135		13.8 %	0.64 [0.46, 0.90]
Total (95% CI)				**100.0 %**	**0.83 [0.75, 0.91]**

Heterogeneity: Chi² = 20.07, df = 7 (P = 0.01); I² =65%

Test for overall effect: Z = 3.92 (P = 0.000088)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 RT + Chemo vs RT alone, Outcome 3 Survival subgroup analysis - age.

Review: Chemotherapy for high-grade glioma

Comparison: 1 RT + Chemo vs RT alone

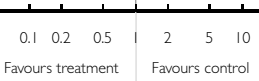
Outcome: 3 Survival subgroup analysis - age

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,99% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,99% CI
za Age - <=40	208/291	163/217		13.6 %	0.74 [0.55, 0.99]
zb Age - 41-59	822/914	656/714		55.4 %	0.84 [0.72, 0.96]
zc Age - >=60	449/474	354/362		31.0 %	0.86 [0.71, 1.04]
Total (95% CI)				**100.0 %**	**0.83 [0.76, 0.90]**

Heterogeneity: Chi² = 1.31, df = 2 (P = 0.52); I² =0.0%

Test for overall effect: Z = 4.56 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 RT + Chemo vs RT alone, Outcome 4 Survival subgroup analysis - sex.

Review: Chemotherapy for high-grade glioma

Comparison: 1 RT + Chemo vs RT alone

Outcome: 4 Survival subgroup analysis - sex

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,99% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,99% CI
zd Sex - Female	514/597	360/399		36.5 %	0.84 [0.69, 1.01]
ze Sex - Male	862/981	624/682		63.5 %	0.83 [0.72, 0.95]
Total (95% CI)				**100.0 %**	**0.83 [0.76, 0.90]**

Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.89); I^2 =0.0%

Test for overall effect: Z = 4.22 (P = 0.000025)

Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 RT + Chemo vs RT alone, Outcome 5 Survival subgroup analysis - histology.

Review: Chemotherapy for high-grade glioma

Comparison: 1 RT + Chemo vs RT alone

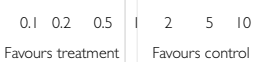
Outcome: 5 Survival subgroup analysis - histology

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,99% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,99% CI
zf Histology - AA	228/297	196/228		19.5 %	0.78 [0.60, 1.02]
zg Histology - GBM	1005/1074	686/719		75.0 %	0.80 [0.70, 0.92]
zh Histology - Other	64/106	59/77		5.5 %	0.71 [0.43, 1.18]
Total (95% CI)				**100.0 %**	**0.79 [0.73, 0.87]**

Heterogeneity: Chi^2 = 0.39, df = 2 (P = 0.82); I^2 =0.0%

Test for overall effect: Z = 5.03 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1 RT + Chemo vs RT alone, Outcome 6 Survival subgroup analysis - performance status.

Review: Chemotherapy for high-grade glioma

Comparison: 1 RT + Chemo vs RT alone

Outcome: 6 Survival subgroup analysis - performance status

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,99% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,99% CI
zi P Status - Good	626/742	519/587		53.6 %	0.83 [0.70, 0.97]
zj P Status - Poor	685/752	416/439		46.4 %	0.80 [0.68, 0.95]
Total (95% CI)				**100.0 %**	**0.82 [0.75, 0.89]**

Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² =0.0%

Test for overall effect: Z = 4.47 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.7. Comparison 1 RT + Chemo vs RT alone, Outcome 7 Survival subgroup analysis - extent of resection.

Review: Chemotherapy for high-grade glioma

Comparison: 1 RT + Chemo vs RT alone

Outcome: 7 Survival subgroup analysis - extent of resection

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,99% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,99% CI
zk Rsection-Complete	341/398	264/292		26.2 %	0.74 [0.59, 0.93]
zl Rsection- Incompl	830/947	529/576		56.0 %	0.82 [0.71, 0.96]
zm Rsection - Biopsy	196/221	176/197		17.8 %	0.92 [0.70, 1.21]
Total (95% CI)				**100.0 %**	**0.82 [0.75, 0.89]**

Heterogeneity: Chi² = 2.54, df = 2 (P = 0.28); I² =21%

Test for overall effect: Z = 4.55 (P < 0.00001)

Test for subgroup differences: Not applicable

ADDITIONAL TABLES

Table 1. Patient Characteristics

		RT + Chemotherapy	RT alone	Total
Age	<=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
	Unknown	18 (1%)	12 (1%)	30
Histology	AA	400 (24%)	306 (24%)	706
	GBM	1062 (62%)	838 (64%)	1900
	Other	98 (6%)	80 (6%)	178
	Unknown	138 (8%)	82 (6%)	220
Performance Status	Good	636 (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

Table 2. Baseline survival and equivalent absolute increases

		1 yr survival	1 yr survival	2 yr survival	2 yr survival
		Baseline	Absolute increase	Baseline	Absolute increase
Age	<=40	78%	3%	50%	5%
	41-49	45%	6%	14%	5%
	>=60	22%	6%	4%	2%
Sex	Male	45%	6%	18%	5%
	Female	40%	6%	16%	5%
Histology	AA	58%	5%	31%	6%
	GBM	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%

WHAT'S NEW

Last assessed as up-to-date: 31 July 2003.

Date	Event	Description
21 July 2009	Review declared as stable	IPD data

HISTORY

Review first published: Issue 4, 2002

Date	Event	Description
13 October 2008	Amended	Converted to new review format.
21 May 2002	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

All reviewers participated in the design, execution and analysis of the review.

DECLARATIONS OF INTEREST

None known

NOTES

This review originated as an individual patient data (IPD) review, therefore the text has been agreed upon by the collaborative group who undertook the review.

The manuscript has been scrutinised by the collaborative group and has been through peer review prior to publication in a journal as well as being assessed by the Cochrane Review Group.

Searches will be updated according to usual Cochrane guidelines, however, the analyses will only be updated if substantial new evidence emerges.

INDEX TERMS

Medical Subject Headings (MeSH)

Combined Modality Therapy; Glioma [*drug therapy; *radiotherapy; surgery]; Randomized Controlled Trials as Topic

MeSH check words

Humans