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Chemotherapy wafers for high grade glioma (Review)

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[Intervention Review]

Chemotherapy wafers for high grade glioma

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ABSTRACT

Background

Standard treatment for high grade glioma (HGG) usually entails surgery (either biopsy or resection) followed by radiotherapy plus or minus temozolomide. Implanting wafers impregnated with chemotherapy agents into the resection cavity represents a novel means of delivering drugs directly to the resection cavity with potentially fewer systemic side effects. It is not clear how effective this modality is or whether it should be recommended as part of standard care for patients with HGG.

Objectives

To estimate the clinical effectiveness of chemotherapy wafers for patients with HGG.

Search methods

The following databases were searched: CENTRAL (issue 4, 2010); MEDLINE and EMBASE. The original search strategy also included: Science Citation Index; Physician Data Query; and the meta-Register of Controlled Trials. Reference lists of all identified studies were searched. The Journal of Neuro-Oncology and Neuro-oncology were hand searched from 1999 to 2010, including all conference abstracts. Neuro-oncologists, trial authors and drug manufacturers were contacted regarding ongoing and unpublished trials.

Selection criteria

Patients included those of all ages with a histologically proven diagnosis of HGG (using intra-operative analysis when undergoing first resection). Therapy could be instigated for either newly diagnosed disease (primary therapy) or at recurrence. Interventions included insertion of chemotherapy wafers to the resection cavity. Included studies had to be randomised controlled trials (RCTs).

Data collection and analysis

Two independent review authors assessed the search results for relevance and undertook critical appraisal according to pre-specified guidelines.

Main results

In primary disease two RCTs assessing the effect of carmustine impregnated wafers (Gliadel®) and enrolling a total of 272 participants were identified. Survival was increased with Gliadel® compared to placebo (hazard ratio (HR) 0.65, 95% Confidence Interval (CI) 0.48 to 0.86, $P = 0.003$). In recurrent disease a single RCT was included comparing Gliadel® with placebo and enrolled 222 participants. It did not

demonstrate a significant survival increase (HR 0.83, 95% CI 0.62 to 1.10, $P = 0.2$). There was no suitable data for any of the secondary outcome measures. Adverse events were not more common in either arm and are presented in a descriptive fashion.

Authors' conclusions

Carmustine impregnated wafers (Gliadel®) result in improved survival without an increased incidence of adverse events over placebo wafers when used for primary disease therapy. There is no evidence of benefit for any other outcome measures. In recurrent disease Gliadel® does not appear to confer any additional benefit.

PLAIN LANGUAGE SUMMARY

Treatment of high grade glioma with anti-cancer drug (chemotherapy) coated implants

High grade glioma is a rapidly progressive form of brain tumour. Standard therapy involves the use of surgery (either biopsy or resection) and radiotherapy plus or minus temozolomide. Chemotherapy was not previously used due to concerns over efficacy and high risks of side effects.

We found two trials, enrolling 272 people in total, with newly diagnosed high grade glioma, that studied the effects of implanting wafers coated with an anti-cancer drug called carmustine (Gliadel®) in the area where the tumour was removed. This was compared with implanting wafers that contained no drug. Both groups received radiotherapy afterwards. Patients who received carmustine wafers had a longer survival without a demonstrably higher incidence of adverse events (side effects).

A similar trial enrolled 222 people who had already been diagnosed with a high grade glioma and received surgery but had then had a relapse of disease. In this situation the trial found that Gliadel® did not improve survival or any other outcome measure looked at.

BACKGROUND

Description of the condition

Gliomas are tumours of the brain and spinal cord, so called because they develop from the glial cells which form structures that surround and support neurons. Gliomas are graded by the World Health Organisation classification on a scale of I to IV, based on the histological appearance of the tumour (Kleihues 1993). High grade gliomas (HGG) belong to grades III or IV and have in common an aggressive and infiltrating nature. The majority of HGG are of the sub-types Glioblastoma Multiforme (GBM), Anaplastic Astrocytoma (AA) and Anaplastic Oligodendrocytoma (AO). The incidence of HGG is around 8 per 100,000 per year, resulting in around 4800 new cases in the UK each year (Counsell 1996). Overall, HGG make up about one percent of all new tumours types (SHS 2009).

In general, HGG have a poor prognosis. They are rapidly progressive and resistant to therapy. Their infiltrating nature means they cannot be completely excised and the majority will recur within 2cm of their original location (Hochberg 1980). Median survival is around one year for GBM, two years for AA and five years for AO (Winger 1989). Curative therapy is rarely possible necessitating that current therapies should emphasise symptomatic improvement and quality of life (QoL). Glucocorticosteroids constitute a fundamental, predominantly symptomatic, component of management (Kaal 2004). Surgery can take the form of biopsy or more aggressive craniotomy and resection. Currently there is no quality evidence from RCTs that either approach is better than the other but resection is commonly attempted where feasible (Hart 2000). Radiotherapy is the core therapeutic modality and has a substantial evidence basis (Grant 2004); it increases median survival from three to four months to around nine to ten months (Walker 1978).

Description of the intervention

Many RCTs have been performed using various different chemotherapy regimes, the most common being a nitrosurea based regime of Procarbazine, Lomustine (CCNU) and Vincristine (PCV). The results have generally been conflicting, although a meta-analysis has demonstrated a statistically significant increase in survival with chemotherapy (HR 0.85 CI 0.78 to 0.92 $P < 0.0001$), which translates into roughly a two month increase in median survival to around 12 months (GMT Group 2002). It is not clear whether the gain in survival reflects a useful period of good quality of life (QoL).

During the later part of the last decade the oral alkylating agent Temozolomide has been approved for use in primary therapy of GBM under selected circumstances. A non-placebo controlled randomised trial found temozolomide to be efficacious as part of first line therapy in prolonging survival and increasing time to progression in selected patients when given together with radiotherapy and for up to six months thereafter (Stupp 2005). Temozolomide is now becoming part of the standard oncological repertoire for histologically confirmed GBM in the primary disease setting in selected patients, although side effects including haematological toxicity are not infrequent and long term effects are unknown.

How the intervention might work

The most studied type of implantable chemotherapy wafer is Gliadel®. This is a local therapy designed to be left on the tumour bed at resection and provides a controlled release of 7.7mg carmustine over a period of around 5 days (Fleming 2002). In theory this should reduce systemic toxicities and allow a greater dose to be provided to residual tumour than PCV chemotherapy. Wafer implantation at the time of surgery would also simplify subsequent management logistics compared to systemic chemotherapy which is usually given over a course of around six months. Early phase II series noted Gliadel® was a safe treatment for use in GBM with notably good survival (Brem 1995; Kleinberg 2004).

Why it is important to do this review

Despite these proposed advantages it is not clear whether to recommend Gliadel® or any other chemotherapy wafer for HGG as either primary therapy or for recurrent disease.

OBJECTIVES

To assess the effectiveness of implantable chemotherapy wafers for HGG as part of;

- Therapy for primary disease (i.e. first treatment at initial diagnosis);
- Therapy for recurrent disease (i.e. previously treated HGG)

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) meeting the selection criteria (described in detail below). Ideally studies should be double-blinded and placebo-controlled although this was not a strict entry criteria. Non-English language articles were eligible for inclusion.

Types of participants

- Therapy for primary disease:

Patients with a presumed HGG from clinical examination and imaging (CT and/or MRI) were included. Additional imaging modalities e.g. Positron Emission Tomography (PET) or Magnetic Resonance Spectroscopy (MRS) were not mandatory. Patients have been stratified for age, performance status and histology (the main prognostic factors) in order to provide comparable treatment arms. Performance status was recorded using the Karnofsky Performance Score (KPS) (Karnofsky 1948) or World Health Organisation (WHO) score (WHO 1982). Intra-operative histology, using for example frozen section or smear, was mandatory to confirm the provisional diagnosis of 'malignant glioma' prior to wafer insertion, to ensure patients with other diagnoses were not included (final histological analysis can be given subsequently).

- Therapy for recurrent disease:

Patients with a previously treated and histologically confirmed (either through biopsy or resection) HGG. Prior therapy including radiotherapy or chemotherapy. The definition of recurrent disease should be using open and thorough criteria should be used to define recurrence according to clinical symptoms, imaging and

increasing steroid therapy (Wen 2010). The use of PET, MRS or imaging modalities other than structural MRI and CT will be left to the treating clinicians discretion.

Types of interventions

Intervention

- Surgical resection and implantation of chemotherapy wafer(s) to the tumour cavity.

Resection is often graded as either attempted total, partial, or palliative de-bulking; all of which are eligible for inclusion. Assessment of complete resection can be by the surgeons operating opinion but ideally by early post-operative imaging (Hensen 2008). All aids to achieving surgical resection - including neuro-navigation, 5-ALA/Gliolan® guided resection, Sonowand® and intra-operative MRI - were be eligible for inclusion. A histologically complete resection was believed to be unlikely given that HGG can be found to have infiltrated beyond the contrast-enhancing lesion seen on CT scan (Devaux 1993; Kreth 1993; Nazarro 1990).

Comparison

- Surgical resection and implantation of placebo wafer or no wafer.

Post-operative therapy was not directly assessed but in light of the known effectiveness of certain treatments a treatment algorithm was desirable ideally conforming to known standards (Grant 2004; Rampling 2005). This should include: medical management of seizures and other symptoms; glucocorticosteroids for brain oedema, symptoms of raised intra-cranial pressure or focal deficits; radiotherapy according to accepted guidelines. Chemotherapy (PCV, temozolomide or other) in either arm is left to the discretion of the individual attending clinician.

Types of outcome measures

Primary outcomes

- Survival: from time of randomisation until death or censoring

Secondary outcomes

- Time To Progression (TTP) or Progression Free Survival (PFS): open and thorough criteria was used to define recurrence according to clinical symptoms, imaging and increasing steroid therapy (Wen 2010).
- Quality of Life (QoL): a reliable and objective grading measure was used, for example the EORTC QLQC30/BN-20 and FACT-BrS (Mauer 2008)
- Symptom control: improvement of symptoms, or a prolonged maintenance of symptoms without deterioration.
- Adverse events: nature (as defined using MedDRA (Medical Dictionary for Regulatory Authorities criteria) and timing (MedDRA 2008). Examples include: haematoma, wound complications, infection (and site), CSF leak, oedema, seizures and general medical complications. Further procedures required for complications should be noted. Both the total number of complications and complications per patient should be stated.
- Mortality: cause specific immediately following procedure and at 30 day.

Search methods for identification of studies

Electronic searches

Up to November 2010 the following search databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL, Issue 4, 2010), MEDLINE and EMBASE. The full search strategies are described in the [Appendices](#). Foreign language journals were eligible for inclusion. The following databases were searched for the original review in 2007: The Cochrane Central Register of Controlled Trials (CENTRAL, Issue 2, 2007), MEDLINE, EMBASE, Science Citation Index (SCI), Physician Data Query (PDQ) and the meta-Register of Controlled Trials (mRCT).

The same principle was used to search each database. Firstly the terms and phrases identifying randomised controlled trials were combined using the Boolean "OR". Secondly, all the terms and phrases describing malignant glioma, were combined with "OR". Thirdly, everything used to identify the interventions of interest was combined with "OR". These three initial search results were then grouped with the Boolean operator "AND" and the results displayed. Wild cards and truncation symbols were used to ensure terms with alternative spellings and/or endings were not missed. MeSH terms were exploded.

Searching other resources

The references of all included studies were searched to identify additional trials.

Hand search

A hand search of the Journal of Neuro-Oncology and Neuro-oncology from 1991 to 2010 was undertaken in order to identify trials that may not have been present in the electronic databases. This included searching all conference abstracts published in the journal.

Personal communication

The manufacturer of Gliadel® (Guilford Pharmaceuticals, now owned by MGI Pharma) and its UK distributor (Link Pharmaceuticals) were contacted regarding any further RCTs involving their product. As they are the sole manufacturer of Gliadel® it was believed that they would be aware of all research involving their product.

The following contact authors of each of the included RCTs were contacted for information on any on-going or commencing studies: Dr Henry Brem (John Hopkins Hospital, Baltimore, USA), Dr Simo Valtonen (Turku University Central Hospital, Turku, Finland), Dr Manfred Westphal (University Hospital Eppendorf, Hamburg, Germany).

The following experts in neuro-oncology were also asked for email feedback on any on-going or commencing studies or any protocols in evolution: Dr Michael Weller (University Hospital Zurich, Switzerland), Prof Wolfgang Wick (Heidelberg, Germany), Dr Susan Short (University College Hospital, London) and Dr Roger Stupp (University of Lausanne, Switzerland).

Data collection and analysis

Selection of studies

Identification of studies was made in two stages. Abstracts returned by the original search were examined independently by two review authors (MGH and RG). Those studies that clearly did not meet the inclusion criteria were excluded and copies of the full text of potentially relevant references were obtained. Next, full texts of the selected references were obtained and further examined independently by two review authors (MGH and RG) for inclusion or exclusion criteria. At all times any disagreements were resolved through discussion. If sufficient data was not available for assessment then the relevant authors of the trials were contacted.

Data extraction and management

For included studies, two review authors independently abstracted data on characteristics of patients and interventions, study quality, endpoints and deviations from protocol using a pre-specified form designed to complete the information required for the table of [Characteristics of included studies](#), [Table 1](#) and [Table 2](#). Differences were reconciled by discussion or by consultation with a third review author.

Assessment of risk of bias in included studies

Trials deemed relevant were critically appraised according to checklist ([Fowkes 1991](#)) and the criteria reported in the NHS CRD Report No. 4 ([CRD 2009](#)). Tables were constructed to summarise internal and external validity ([Juni 2001](#)). Trials were allocated according to risk of bias as described in the Cochrane Handbook ([Higgins 2009](#)). Critical appraisal was done by two independent review authors (MGH and RG). Any disputes were resolved through discussion.

Measures of treatment effect

- Time to event data (survival and TTP/PFS): the Hazard Ratio (HR) and its inverse variance were abstracted
- Continuous outcomes (QoL and symptom control): the final value and standard deviation of the outcome of interest in each treatment arm at the end of the follow-up were abstracted
- Dichotomous outcomes (AE and mortality): the number of patients in each treatment arm who experienced the outcome of interest were abstracted in order to estimate a Relative Risk (RR)
- Dichotomous and continuous data: we abstracted the number of patients assessed at each endpoint.

Where possible, all data abstracted were those relevant to an intention to treat (ITT) analysis. In the case of missing data required for the review outcomes, the study authors were contacted. Data extraction was performed by two review authors (MGH and RG) and integration to RevMan by a single review author (MGH).

Unit of analysis issues

If the HR and its variance were not presented we attempted to abstract the data required to estimate them ([Parmar 1998](#)).

Dealing with missing data

In the case of missing data required for the review outcomes the study authors were contacted.

Assessment of heterogeneity

Visual inspection of forest plots in combination with the Chi-squared test will be used to gauge whether trials are of sufficient homogeneity to be combined in meta-analysis.

Assessment of reporting biases

A funnel graph of trial effect versus trial size was to be constructed with the data from all included studies entered in order to investigate the likelihood of publication bias.

Data synthesis

We pooled the results of trials of primary therapy and therapy for recurrent disease in separate meta-analyses.

- For time to event data, HRs were pooled using the generic inverse variance facility of RevMan 5.0.
- For dichotomous outcomes calculated the relative risk (RR) for each study and then pooled the RRs.
- For continuous outcomes we pooled the weighted mean differences between the treatment arms at the end of follow-up using the mean difference method if all trials have measured the outcome on the same scale, or using the standardised mean difference method otherwise

Both random and fixed effects models were used in the meta-analysis ([DerSimonian 1986](#)).

In light of the known benefits of chemotherapy in primary disease, we had planned to assign trials including systemic chemotherapy in the control arm to a separate sub-group and pool results of sub-groups if they showed consistent findings.

If sufficient studies were available, we had planned to construct a funnel plot of treatment effect versus precision with the data from all studies included in order to investigate the likelihood of publication bias.

Subgroup analysis and investigation of heterogeneity

In light of the known benefits of chemotherapy in primary disease we had planned to assign trials including chemotherapy to a separate subgroup analysis.

A funnel plot of treatment effect versus precision with the data from all studies included was proposed if sufficient studies were identified in order to investigate the likelihood of publication bias.

Sensitivity analysis

Studies that included objective blinded early post-operative MRI in their assessment of extent of resection were to be subjected to a subsequent sensitivity analysis.

Both fixed and random effects models were to have been performed to determine the robustness of the results.

RESULTS

Description of studies

The 2010 update identified the following number of total hits for each search engine:

- Medline: 606 references

- Embase: 765 references
- Central: 122 references

Results of the search

The search strategy identified 121 potentially relevant references which were screened online. We excluded 112 references and retrieved 9 for detailed evaluation. The updated search strategy revealed potentially relevant references of which 1 is noted in the table of excluded studies.

Included studies

The three included studies are described in detail in the table of [Characteristics of included studies](#).

Primary therapy

Two studies (reported by three articles) met the inclusion criteria.

The first trial was set in four Scandinavian neurosurgical hospitals and recruited 32 patients between 1992 and 1993 ([Valtonen 1997](#)). It included patients (entry criteria aged 18 to 65) who had a good Karnofsky Performance Score (KPS) ([Karnofsky 1948](#)) at baseline (KPS 60 or more). It studied Gliadel wafers or identical placebo wafers not coated in carmustine implanted after resection when HGG was confirmed on intra-operative frozen section. Further management in both arms included radiotherapy but not systemic chemotherapy. The trial was blinded to participants, treatment providers and outcome assessors. Placebo control was adequately concealed. Therapy for recurrence was not specified in advance. The primary outcome was survival; secondary outcomes included adverse events and mortality. It was terminated prematurely due to difficulty in sourcing new wafers.

The second and largest trial recruited 240 patients from multiple centres throughout Europe between 1997 and 1999 ([Westphal 2003](#)). The remaining study criteria were almost identical to those of the earlier trial. Further secondary outcome measures included PFS, time to neuro performance measure decline, and median time to decline of Karnofsky performance score (defined as a change of 10 or more in KPS). A follow up paper presented long term data relating to survival using alternative statistical methods ([Westphal 2006](#)).

Therapy for recurrence

One trial met the inclusion criteria ([Brem 1997](#)). It was set in 27 neurosurgical centres in the USA and Canada and recruited 222 patients between 1989 and 1992. It included all people who had previously confirmed HGG treated with surgery and radiotherapy. Recurrence was defined on radiological criteria alone. The interventions were maximal resection followed by implantation of Gliadel wafer or identical placebo wafer not coated in carmustine. All participants, treatment providers and outcome assessors were blinded to study group. As the maximal dose of radiation was given no further radiotherapy was available as a treatment option. Following intervention subsequent treatment including chemotherapy was given as required and not according to a pre-defined protocol. The primary outcome was survival; secondary outcome measures included adverse events and mortality.

Excluded studies

We excluded nine studies for the following reasons:

- A meta-analysis of Gliadel® for primary therapy ([Mulrow 2003](#); [Perry 2007](#); [Garside 2007](#))
- A web based publication for a university technology assessment unit ([Brophy 2004](#));
- A web based transcript of the FDA assessment of Gliadel® ([FDA 2003](#))
- Two phase III studies of wafers other than Gliadel® that did not clearly meet our inclusion criteria ([Dalbasti 2002](#); [Sheleg 2002](#));
- A phase II study of Gliadel® ([Brem 1995](#))
- A Phase II study of Gliadel® and Temozolomide combination therapy ([LaRocca 2006](#))

Risk of bias in included studies

A full analysis of the internal validity of the included studies is presented in [Table 1](#) and summarised below.

Primary gliadel therapy

The design characteristics and internal validity of both trials were almost identical ([Valtonen 1997](#); [Westphal 2003](#); [Westphal 2006](#)).

- **Allocation:** the actual methods of randomisation were not fully described and are a potential area for bias. Background characteristics: both treatment arms were similarly matched at baseline. The trial by [Westphal 2003](#) had a difference in the number of Grade III tumours in each arm (13 in the Gliadel arm and 8 in the Placebo arm). Final analysis of histological subtype was performed after randomisation and provision of treatment meaning it would not have been possible for this discrepancy to affect the arm a participant was assigned to i.e. there was no risk of allocation bias depending on tumour grade. Simply put, it is unlikely that anyone involved in the trial could have deliberately included more Grade III tumours in the Gliadel® arm. The authors use of blinded central pathological review is to be commended. Discrepancy of this kind in the baseline characteristics of treatment groups should be minimised by combination in meta-analysis. Nevertheless, this inequality in baseline characteristics could account for some difference in baseline prognosis i.e. non-treatment related effect.
- **Blinding:** good attention was given to conceal treatment allocation and blind all those involved to treatment groups. In particular the placebo wafer was essentially identical to Gliadel® although some publications suggest subtle differences with the placebo wafer ([FDA 2003](#)).
- **Incomplete outcome data:** analysis was on an ITT basis, with all patients accounted for and all withdrawals specified. In the trials [Westphal 2003](#) and [Westphal 2006](#) the outcome measures of PFS and QoL used were subjective. The use of time to decline in Karnofsky Performance Status as a marker of progression is not an accurate indicator of progression, as many other factors other than recurrence can affect KPS, hence this was not included in the results. The use of time to decline in neuro performance indicators was not specified as a valid measure of progression or QoL and hence was also not included in the final analysis.
- **Selective reporting:** the choice of stratification by country in the statistical methods of the original article was incorrect, although this was amended in the later article. Survival data is taken from the later trial only in light of this. Adverse events in all the included studies contained serious methodological flaws. The trial by [Valtonen 1997](#) chose to report adverse event rates descriptively rather than in tables. The article by [Westphal 2003](#)

did provide a table of individual nervous system adverse events (occurring in greater than 5% of participants) for each arm but not for total events. There was no attempt to discuss the severity of events and the number of patients who had multiple episodes i.e. only total numbers of events were specified rather than the risk for each patient. Therefore it is not possible to provide a detailed description of adverse events according to our specified outcome criteria.

- **Other potential sources of bias:** 'total resection' was reported in up to 50% in one RCT (Westphal 2003). The rates of total resection vary within the literature depending largely due to the detection mechanism making the significance of this statistic hard to interpret. There wasn't a significant difference between arms that could confer bias.
- Despite the flawed methods involved in collecting PFS/TTP data the largest RCT did not demonstrate a difference between arms: this opens up the possibility that a significant benefit to the survival times might have arisen in the management of recurrent disease. Post-operative management: at recurrence management was aggressive with up to 30% receiving re-operation. As the methods of blinding were stringent it is unlikely that obvious bias could have arisen at this point. Most patients received PCV chemotherapy after radiotherapy, which wasn't always standard practice, in the UK at least.
- Inclusion/exclusion criteria were well thought out and clearly stipulated. The inclusion criteria 'lesions suitable for surgery' does add some ambiguity to patient selection.

There were no significant methodological differences between the trials to prevent pooling their results in meta-analysis. Both included trials were deemed to be at an acceptably low risk of bias and eligible for inclusion.

Gliadel for recurrence

- **Allocation:** methods of randomisation were not described fully and are a potential area for bias. Background characteristics and the prognostic factors were well distributed between arms.
- **Blinding:** good attention was given to blind all those involved in treatment group. In particular the placebo wafer used was almost identical to Gliadel® although some have suggested there were subtle differences (FDA 2003).
- **Incomplete outcome data:** analysis was stated to be on an ITT basis but not all patients or withdrawals were specified. There was incomplete reporting of results regarding QoL data which meant the data was not presented in the article.
- **Selective reporting:** adverse events were presented in a descriptive fashion rather than in tables. It was not clear what the overall adverse event rates were or if single patients suffered multiple events.
- **Other potential sources of bias:** the use of the statistical model to define a treatment population where Gliadel® would have maximum effect is of questionable significance given the already highly selected nature of participants and the hypothetical data produced i.e. using prognostic factors rather than actual patient outcomes. Recurrence was defined using radiological criteria alone rather than using more accurate clinical and radiological criteria (Wen 2010). There is doubt therefore as to whether all patients had true recurrent disease or merely changes on imaging that could be confused with radiation necrosis.

Inclusion and exclusion criteria were prescriptive except that the surgeon had to deem another tumour resection was worthwhile.

Effects of interventions

Primary therapy

Gliadel® resulted in an increase in survival compared with placebo (HR 0.65, CI 0.48 to 0.86, $P = 0.003$). The results for the random effects model were HR 0.49, CI 0.19 - 1.23, $P = 0.13$. Weightings for the smaller study were approximately 10% in the fixed effects model and 40% in the random effects model. The inclusion of only two studies is probably too few for the random effects model to provide an accurate estimate of the width of distribution of intervention effects. Fixed effects models were used for reporting summary statistics as the entry criteria for each study were broadly inclusive and intervention effects similar for each of the two trials. A formal statistical test of heterogeneity was deemed unnecessary due to the presence of only two trials that demonstrated broadly congruent treatment effects. No data was retrievable for analysis of TTP/PFS, QoL or symptom control.

Adverse events are presented in a descriptive manner due to the low number of events and variability in reporting. Neither study reported any perioperative mortality. In the Valtonen study adverse events included total event rates of 12/16 (75%) of Gliadel® patients and 9 out of 16 (56%) of placebo patients (non-significant) (Valtonen 1997). The Westphal 2003 and 2006 data recorded the total number of complications was: cerebral oedema 42 (Gliadel® 23 versus Placebo 19); intra-cranial hypertension 11 (Gliadel® 9 versus Placebo 2); healing abnormalities 28 (Gliadel® 16 versus Placebo 12); infections 11 (Gliadel® 5 versus Placebo 6); seizures 71 (Gliadel® 33 versus Placebo 38); and thromboembolic events 35 (Gliadel® 18 versus Placebo 17). Only intra-cranial hypertension was statistically more common in the Gliadel® arm ($P = 0.019$).

Therapy for recurrence

Gliadel® did not confer any survival benefit over placebo (HR 0.83, CI 0.62 to 1.10, $P = 0.2$). There was no data available from the trials to calculate TTP/PFS or QoL. Adverse events included no perioperative mortality in either arm. There was no statistically significant difference in the rates of the rates of individually specified adverse events. Acute numbers include: 5 infections (Gliadel® 4, Placebo 1); 38 seizures (Gliadel® 19, Placebo 19); 19 healing abnormalities (14 Gliadel®, 5 placebo); and 10 intra-cranial hypertension (4 Gliadel®, 6 placebo).

As only three studies were included we did not construct a funnel plot.

DISCUSSION

The study indicates a survival benefit for the use of Gliadel® and radiotherapy compared to radiotherapy alone as part of primary therapy in highly selected patients. Although the HR remains the most appropriate statistic to present survival data due to censoring, clinicians are often more familiar with median survivals and survival percentages at fixed time points. Overall Gliadel® resulted in a 35% risk reduction for death. The trials suggest a median survival with Gliadel® of around 14 months with a 2.5 month improvement over placebo. Survival is around 10% better with Gliadel® at 1 and 2 years, although analysis of the survival curves from the individual trials suggests that the increase in

survival occurs mainly after one year. These figures are similar to those seen in the meta-analysis of PCV chemotherapy (Stewart 2002) and the largest RCT with temozolomide (Stupp 2005).

There is not a demonstrable survival benefit for the use of Gliadel® in recurrent disease. Analysis of the survival curve in the included study suggests no difference between arms. Survival after recurrence is usually short, with a median of around six months. At recurrence GBM may have developed a resistance to chemotherapy by this point, making even local application of carmustine ineffective. Local factors such as radiotherapy induced changes and gliosis may limit the diffusion of chemotherapy around the resection margin in recurrent disease.

Data presentation for secondary outcomes was poor in the included studies, hindering meta-analysis. Time to progression (TTP/PFS) was hindered by a large duration between assessments reducing the sensitivity to a level which may result in missing a difference that was really there. The criteria used for determining progression should have included clinical as well as radiological criteria to improve accuracy (Wen 2010). Collection of QoL data was poor and lead to the discontinuation of this trial outcome in the largest study no doubt reflecting in part the difficulties in collecting this information.

Adverse event rates of Gliadel® were not significantly higher than placebo wafers in all the published RCTs except for intra-cranial hypertension in a single study (Westphal 2003). It is difficult to know the severity and definitions involved in the diagnosis of intra-cranial hypertension in the reporting study making interpretation of the significance of this finding difficult. Actual Phase IV studies or post-approval monitoring data, collected by the manufacturers, is presented in the official Gliadel® handbook. Quoted figures include: healing abnormalities 10%; cerebral oedema 7%; and seizures 5%. Most of the studies were small retrospective case series with many of the problems of adverse event reporting common to those discussed in the RCTs. It is important to note that case reports and small case series have documented isolated cases of severe morbidity or mortality due to Gliadel®. Cases include intra-ventricular dislodgement and acute obstructive hydrocephalus when the ventricles have been opened and 'malignant' cerebral oedema (Gallego 2007; Weber 2005). Although it is not clear whether a wafer itself confers a risk of adverse events above that of standard resection from the evidence presented in the RCTs, the importance of accurate post-marketing surveillance and Phase IV studies to continue to monitor for additional events cannot be over-emphasised.

The inclusion of more Grade III tumours in the Gliadel® arm than the placebo arm of the largest RCT remains a contentious issue. In particular, in the long term follow-up study grade III tumours were disproportionately represented (5 out of 9 in Gliadel® and 2 out of 2 in Placebo) (Westphal 2006). This inequality was noted when pathology was re-examined at a central location, although not all tumours were submitted and final grading was made by a single pathologist. Grade III tumours are known to have a longer survival and increased response to chemotherapy compared with Grade IV tumours, although there is no reliable proof that chemotherapy increases survival in Grade III tumours (Siker 2006). Histological grading is known to differ between pathologists (Castillo 2004) but the initial decision to include patients in the study depending on an intra-operative frozen section diagnosis is valid. As allocation concealment was well maintained it is unlikely that any deliberate

bias could have arisen. For practical purposes the methods of the trial are robust and from an ITT perspective the results are sound. Simply put, it is unlikely anyone involved in the trial could have deliberately recruited more patients with Grade III tumours to the Gliadel® arm in order to produce improved survival figures. Nevertheless, the exact contribution that this inequality in Grade III tumours between arms has is still disputed.

The management for recurrence was aggressive with up to 30% undergoing surgery for recurrence. After primary therapy, the maximal dose of radiotherapy tolerated has already been given, leaving surgery or chemotherapy as the main management options. Chemotherapy is usually preferred in light of the poor prognosis, leaving surgery for those with clear indications such as an easily accessible lesion, obstructive hydrocephalus or raised intra-cranial pressure. Bias at this stage is still unlikely given that management was blinded but the difference in survival after recurrence between arms does open up the possibility that management at this stage could have significantly impacted on the overall trial findings.

The generalisability of the patients and interventions used in the two included studies is summarised in Table 2. All studies recruited patients under 65 years old with a good performance score. This limits the applicability of results to the GBM population as a whole. A study of recruitment in one of the trial centres estimated that around 30% of those presenting would be suitable for consideration of primary Gliadel® therapy (Whittle 2003).

Gliadel® and temozolomide combination therapy for primary disease is a new research avenue being pursued by selected mainly North American institutes (LaRocca 2006). This review did not find any RCTs in the area to document any effectiveness over placebo and standard therapy. The expense and potential toxicity of combined chemotherapy agents are strong reasons to justify RCTs of combination therapy prior to its introduction as part of standard practice.

AUTHORS' CONCLUSIONS

Implications for practice

There is evidence that Gliadel® increases survival in primary therapy for HGG but not for recurrent disease, and that this benefit is without a significant increase in adverse events. There is no evidence of benefit with regards to TTP/PFS or QoL. These findings are based predominantly on two well designed trials with a total of just under 300 patients. In a well selected subgroup of patients presenting with presumed GBM, Gliadel® warrants consideration for use as primary therapy. Decisions on the use of Gliadel® need to be made on an individual basis as part of a multi-disciplinary team discussion (NICE 2007).

Implications for research

Further studies focusing on molecular markers to predict tumour response are needed to better identify those patients who will benefit from Gliadel® (Kim 2006). There is also scope to examine the role of Gliadel® in combination with other therapies, as there is likely to be a synergistic effect due to the multiple pathways involved in tumorigenesis. In all future trials better attention needs to be paid to secondary outcome measures (Mauer 2008), and entry criteria should be expanded to include a broader range of patients with other forms of HGG. A trial comparing Gliadel®

with temozolomide could be warranted in light of similar survival benefits in the same patient population although a review of on-going studies suggests combination therapy appears to be the greater focus of attention.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Brem 1997

Methods	RCT
Participants	222 consecutive patients from 27 centres in the USA and Canada (1/3/89 to 17/1/92). Eligibility criteria: presence of a single unilateral single focus of tumour in the cerebrum showing at least 1.0cm 3 enhancing volume on CT or MRI; KPS 60 or more; completion of external beam radiation therapy; and no nitrosureas for 6 weeks and no other systemic chemotherapeutic agent for 4 weeks before enrolment. In addition, patients' surgeons made an independent determination that another tumour resection would be done irrespective of the study. Ineligibility criteria; not stated
Interventions	Up to eight discs of Gliadel or identical placebo wafer applied to the resection cavity. Post-operative radiotherapy was administered to both arms according to protocol. Further treatment was given as necessary.
Outcomes	Primary: Survival Secondary: rates of complications, toxicity, QoL.
Notes	All patients: median survival 31 versus 23 weeks; HR 0.83, CI 0.63 to 1.10 P = 0.19 All patients survival at 6 months: 53% versus 40%, P = 0.061 All patients Cox model: HR 0.67 CI 0.51 to 0.9 P = 0.006 GBM subgroup analysis: HR 0.81 P = 0.22 GBM subgroup Cox model: HR 0.67 CI 0.48 to 0.95 P = 0.02 Adverse events: no peri-operative mortality. Intra-cranial infection cases: 4 (Gliadel) versus 1 (Placebo). Seizure cases: 41 (Gliadel) versus 32 (Placebo).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Awaiting feedback from trial authors

Chemotherapy wafers for high grade glioma (Review)

Brem 1997 (Continued)

Allocation concealment (selection bias)	Unclear risk	Awaiting feedback from trial authors
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo wafers appeared similar to Gliadel although some subtle differences may remain (FDA 2003)
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	High risk	Statistical methods used have the potential to add 'noise'

Valtonen 1997

Methods	RCT
Participants	32 consecutive patients from 4 Scandinavian University hospital neurosurgery units (03/1992 to 03/1993). Inclusion criteria: age 18 to 65 years; Grade III or IV tumour; KPS of 60 or more, and; unilateral, unifocal tumour of at least 1 cm in diameter. Exclusion criteria: significant renal, hepatic or haematological dysfunction; other concomitant life threatening disease; pregnancy; hypersensitivity to radiographic contrast media, and; evidence of systemic disease.
Interventions	Intra-operative placement of 8 or fewer Gliadel or identical placebo wafers (i.e. 61.6mg or less of BC-NU). Radiotherapy: 'standard' RT (not detailed) was given to both arms post-operatively. Further management was provided according to need.
Outcomes	Primary: Survival. Secondary: 2 year survival.
Notes	Median survival: Gliadel 58.1 (42 to undetermined) versus Placebo 39.9 (37.6 to 45) weeks Cox model for time from surgery to death for all patients; HR 0.27, CI 0.11 to 0.68, P = 0.006 Subgroup analysis for survival of GBM only patients Cox model for time from surgery to death for GBM only patients; HR 0.27, CI 0.10 to 0.71, P = 0.008 Adverse events: no peri-operative mortality. 21 complications (Gliadel 12, Placebo 9). No QoL or time to progression data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Awaiting feedback from trial authors
Allocation concealment (selection bias)	Unclear risk	Awaiting feedback from trial authors
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo wafers appeared similar to Gliadel although some subtle differences may remain (FDA 2003)

Chemotherapy wafers for high grade glioma (Review)

Valtonen 1997 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	
Other bias	Unclear risk	Unclear why there was difficulty in sourcing wafers which led to the early termination of the study.

Westphal 2003

Methods	RCT
Participants	240 consecutive patients from 38 centres in 14 countries (12/1997 to 07/1999). Inclusion criteria were: age 18 to 65 years; Grade III or IV tumour; KPS of 60 or more; single, contrast enhancing unilateral supratentorial tumour, and; surgery within 2 weeks of baseline MRI. Exclusion criteria were: prior cytoreductive therapy; prior radiotherapy to the brain; known hypersensitivity to nitrosureas, and; 'clinically significant laboratory abnormalities.'
Interventions	Intra-operative placement of 8 or fewer Gliadel or identical placebo wafers (i.e. 61.6mg or less of BC-NU). Radiotherapy: 55 to 60Gy in 30 to 33 daily fractions 5 days a week to a focal area with a 2 to 5 cm margin for both arms. Further management was provided according to need.
Outcomes	Primary: Survival. Secondary: Time to KPS decline; Time to Neurological Progression; PFS: QoL: Adverse events.
Notes	Median survival: Gliadel 13.9 versus Placebo 11.6 months; HR 0.71 CI 0.52 to 0.96 P = 0.03 (stratified by country) 1 year survival: Gliadel 59.2 versus Placebo 49.6% Cox model for survival in all patients Kaplan-Meier censoring for re-operation; median survival Gliadel 14.6 versus Placebo 11.4, HR 0.64, CI 0.45 to 0.92, P = 0.01 GBM only subgroup analysis; median survival Gliadel 13.5 versus Placebo 11.4, HR 0.76, CI 0.55 to 1.05, P = 0.01 Cox model for GBM subgroup; HR 0.69, CI 0.03 to 0.51, P = 0.04 KPS median time to decline: Gliadel 11.9 versus Placebo 10.4. Deterioration at 1 year: Gliadel 47.5 versus Placebo 39.3 Neuroperformance measures decline: longer time for all measures with Gliadel PFS: 5.9 months both arms, P = 0.9 Adverse events: no peri-operative mortality. Detailed table of neurological adverse events occurring with a frequency of greater than 5%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Awaiting feedback from trial authors
Allocation concealment (selection bias)	Unclear risk	Awaiting feedback from trial authors
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo wafers appeared similar to Gliadel although some subtle differences may remain (FDA 2003)

Westphal 2003 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Statistical methods used stratified for treatment country; this stratification likely increased the statistical significance of the treatment benefit

Westphal 2006

Methods	RCT
Participants	As Westphal 2003
Interventions	As Westphal 2003
Outcomes	As Westphal 2003
Notes	All patients: Median survival Gliadel 13.8 versus Placebo 11.6 months; HR 0.73 CI 0.56 to 0.95 P = 0.018 Survival at 1 year: Gliadel 59% versus Placebo 49%; 2 years: 16% versus 8%; 3 years: 9% versus 2% Cox model for all patients HR 0.75 CI 0.57 to 0.99 P = 0.045 GBM subgroup analysis: median survival Gliadel 13.1 versus Placebo 11.4 months, HR 0.78 CI 0.60 to 1.03 P = 0.08 Cox model for GBM subgroup: HR 0.78 CI 0.58 to 1.05 P = 0.1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Westphal 2003
Allocation concealment (selection bias)	Unclear risk	See Westphal 2003
Blinding (performance bias and detection bias) All outcomes	Low risk	See Westphal 2003
Incomplete outcome data (attrition bias) All outcomes	Low risk	

RCT = Randomised Controlled Trial; KPS = Karnofsky Performance Score; PFS = Progression Free Survival; QoL = Quality of Life.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Brem 1995	This is a prospective phase I trial aimed at assessing the safety of Gliadel wafers as a precept to a full RCT (Westphal 2003). It examined 22 patients in 3 US centres between 07/1990 and 08/1991. The trial was complete when a single centre had randomised 10 patients. Primary outcomes were complications and functional status, secondary outcomes were survival.

Study	Reason for exclusion
Brophy 2004	This is a web based publication assessing Gliadel for primary therapy in HGG. It is undertaken by a University to assess efficacy and costs in a specific region. No meta-analysis is presented.
Dalbasti 2002	Not clearly of RCT design. 40 patients with previous de novo GBM and recurrent disease between January 1997 and December 1999. KPS of 70% or higher. Randomised into control, systemic fote-mustine, bucladesine wafers, or bucladesine wafers with fotemustine.
FDA 2003	Technology appraisal and approval document rather than individual RCT data
Garside 2007	Systematic review and cost-effectiveness appraisal for NICE rather than individual RCT data. This review formed the basis for this Cochrane review and many of the authors are co-authors on this Cochrane review
Kleinberg 2004	This is a retrospective case series of the experience of Gliadel wafers in a single US University hospital oncology centre. It examined 45 patients between 07/1990 and 08/1999. Primary outcome was surgical outcome, secondary outcomes were survival, toxicity, steroid dosing and histopathological findings at re-operation.
LaRocca 2006	Phase II study of Gliadel & Temozolomide primarily assessing safety. Published in abstract form only after presentation at a conference: full publication awaited.
Mulrow 2003	This is a meta-analysis of Gliadel therapy presented as Conference Proceedings. No formal search strategy or systematic review was undertaken.
Perry 2007	Systematic review and meta-analysis of studies rather than an individual RCT
Sheleg 2002	Phase II study. Not RCT.

DATA AND ANALYSES

Comparison 1. Primary Gliadel Therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival	2		HR and variance (Fixed, 95% CI)	0.65 [0.48, 0.86]

Analysis 1.1. Comparison 1 Primary Gliadel Therapy, Outcome 1 Survival.

Study or subgroup	Gliadel N	Placebo N	log[HR and variance] (SE)	HR and variance IV, Fixed, 95% CI	Weight	HR and variance IV, Fixed, 95% CI
Valtonen 1997	16	16	-1.3 (0.474)		9.82%	0.27[0.11,0.68]
Westphal 2006	120	120	-0.3 (0.157)		90.18%	0.71[0.52,0.96]
Total (95% CI)					100%	0.65[0.48,0.86]
Heterogeneity: Tau ² =0; Chi ² =3.75, df=1(P=0.05); I ² =73.31%						
Test for overall effect: Z=2.94(P=0)						
				Favours Gliadel 0.1 0.2 0.5 1 2 5 10 Favours Placebo		

Comparison 2. Gliadel for Recurrence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival	1		HR and variance (Fixed, 95% CI)	0.83 [0.62, 1.10]

Analysis 2.1. Comparison 2 Gliadel for Recurrence, Outcome 1 Survival.

Study or subgroup	Gliadel N	Placebo N	log[HR and variance] (SE)	HR and variance IV, Fixed, 95% CI	Weight	HR and variance IV, Fixed, 95% CI
Brem 1997	110	112	-0.2 (0.145)		100%	0.83[0.62,1.1]
Total (95% CI)					100%	0.83[0.62,1.1]
Heterogeneity: Not applicable Test for overall effect: Z=1.28(P=0.2)						
				Favours Gliadel 0.1 0.2 0.5 1 2 5 10 Favours Placebo		

ADDITIONAL TABLES

Table 1. Internal Validity

Characteristic	Brem 1995	Vuorinen 1997	Westphal 2003 & 2006
Power calculation?	No	Yes (but inadequate recruitment)	Yes
Proper randomisation?	Yes	Unclear	Unclear
Groups similar at baseline?	Yes	No	No
Blinding?	Yes	Yes	Yes
Eligibility criteria stated?	Yes	Yes	Yes
Objective outcome measures?	Some	Some	Some
Analysis on ITT basis?	Yes	Yes	Yes
All patients accounted for	No	Yes	Yes
Withdrawals specified?	No	Yes	Yes (but not from which arm)
Withdrawal reasons given?	No	Yes	Yes
Conflict of interest?	Yes	No	Yes

Table 2. External Validity

Criteria	Westphal 2003 & 2006	Valtonen 1997	Brem 1995
Age (mean and range)	Gliadel: 52.6 (21 to 72). Placebo: 53.6 (30 to 67)	Gliadel: 55.5 (36 to 67). Placebo: 53 (36 to 65).	Gliadel: 48.1 (SD 12.3). Placebo: 47.6 (SD 13.6)
Sex (M:F)	Gliadel 63:37. Placebo 70:30.	Gliadel 50:50. Placebo 63:38.	Gliadel 67:33. Placebo 62:38
Histology	Gliadel: 84% Grade IV, 16% Grade III. Placebo: 88% Grade IV, 12% Grade III.	Gliadel: 69% Grade IV, 31% Grade III. Placebo: 100% Grade IV, 0% Grade III.	Gliadel: 65.5% Grade IV, 17.2% Grade III, 17.2% Other. Placebo: 65.2% Grade IV, 18.8% Grade III, 16.3% Other
KPS (mean and range)	Gliadel: 80 (60 to 100). Placebo: 90 (60 to 100)	Gliadel: 75 (60 to 100). Placebo: 90 (40 to 100).	Gliadel 77 (SD13.1). Placebo: 74.6 (SD12.1)
Extent of Surgery	total resection: Gliadel 47% vs Placebo 41%; partial resection Gliadel 53% vs Placebo 55%; lobectomy Gliadel 2% vs Placebo 3%. Mean % of tumour resection: Gliadel 89.9% vs Placebo 88.3%.	total resection: Gliadel 6% vs Placebo 6%. Partial: Gliadel 88% vs Placebo 94%. Lobectomy: Gliadel 6% vs Placebo 0%.	Gliadel: 79.9% >75% resection. Placebo: 78% >75% resection.
Follow up	Up to 56 months	Greater than 24 months	Up to 200 weeks

APPENDICES

Appendix 1. CENTRAL search strategy

- #1 MeSH descriptor Glioma explode all trees
- #2 glioma*
- #3 astrocytoma*
- #4 oligodendroglioma*
- #5 oligoastrocytoma*
- #6 glioblastoma*
- #7 GBM
- #8 ependymoma*
- #9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
- #10 (#9), from 2006 to 2010

Appendix 2. MEDLINE search strategy

1. exp Glioma/
2. glioma*.mp.
3. astrocytoma*.mp.
4. oligodendroglioma*.mp.
5. oligoastrocytoma*.mp.
6. glioblastoma*.mp.
7. GBM.mp.
8. ependymoma*.mp.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. randomized controlled trial.pt.
11. controlled clinical trial.pt.
12. randomized.ab.
13. placebo.ab.
14. clinical trials as topic.sh.
15. randomly.ab.

16. trial.ti.
17. 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 9 and 17
19. limit 18 to yr="2006 - 2010"

Appendix 3. EMBASE search strategy

- 1 exp glioma/
- 2 glioma*.mp.
- 3 astrocytoma*.mp.
- 4 oligodendroglioma*.mp.
- 5 oligoastrocytoma*.mp.
- 6 glioblastoma*.mp.
- 7 GBM.mp.
- 8 ependymoma*.mp.
- 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
- 10 crossover procedure/
- 11 double blind procedure/
- 12 randomized controlled trial/
- 13 single blind procedure/
- 14 random*.mp.
- 15 factorial*.mp.
- 16 crossover*.mp.
- 17 cross over*.mp.
- 18 cross-over*.mp.
- 19 placebo*.mp.
- 20 (doubl* adj blind*).mp.
- 21 (singl* adj blind*).mp.
- 22 assign*.mp.
- 23 allocat*.mp.
- 24 volunteer*.mp.
- 25 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
- 26 9 and 25
- 27 limit 26 to yr="2006 - 2010"

key:

mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name

Appendix 4. Science Citation Index search strategy

SCIENCE CITATION INDEX (1981 to Jan 2007) Search Strategy

A similar search strategy to the one for Biosis was used. Searches were made in the Title, Keyword or Abstract.

Unlike Biosis, there was no "major concepts" search facility.

The differences were as follows:

1. "tumo*" was used in place of "tumo*r"
2. "central & nervous & system & tumo*" and "central & nervous & system & neoplasm" were two additional searches.
3. "extent & resection" was used in place of "extent of resection"

Appendix 5. Physician Data Query

Physician Data Query (PDQ): <http://www.nci.nih.gov/cancertopics/pdq> (Jan 2007)

Search form - all types of brain tumours - adults, children

Treatment

Active and closed

Phase III and IV

Appendix 6. meta-Register of Controlled Trials (mRCT) search strategy

meta-Register of Controlled Trials (mRCT): <http://www.controlled-trials.com/mrct> (Jan 2007)

Keywords: brain, glioma, gliadel

WHAT'S NEW

Date	Event	Description
17 July 2018	Amended	Next expected date amended
24 May 2018	Review declared as stable	This review is currently not a priority topic area.

HISTORY

Review first published: Issue 3, 2008

Date	Event	Description
11 February 2015	Amended	Contact details updated.
27 March 2014	Amended	Contact details updated.
7 February 2011	New citation required but conclusions have not changed	Final conclusions unchanged but title amended.
20 November 2009	New search has been performed	Updated search strategy and search results amended.
8 May 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Michael G Hart lead and wrote the review.

Ruth Garside ran the original report and was assisted by Gabriel Rogers, Margaret Somerville and Ken Stein. Robin Grant supervised the review and was involved with the final editing process.

Robin Grant came up with the initial review idea and oversaw the final editing process.

DECLARATIONS OF INTEREST

All authors report no conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Cochrane Gynaecological Cancer Review Group Grant, UK.

External sources

- National Co-ordinating Centre for Health Technology Assessment (NCCHTA) for the original Health technology Assessment carried out by PenTAG, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Nil

NOTES

Nil

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents, Alkylating [*administration & dosage]; Brain Neoplasms [*drug therapy] [mortality] [surgery]; Carmustine [*administration & dosage]; Combined Modality Therapy [methods]; Decanoic Acids [administration & dosage]; Drug Carriers [*administration & dosage]; Glioma [*drug therapy] [mortality] [surgery]; Neoplasm Recurrence, Local [drug therapy] [mortality]; Polyesters [administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Humans