Chemotherapeutic wafers for High Grade Glioma (Review)

Hart MG, Grant R, Garside R, Rogers G, Somerville M, Stein K

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[Intervention Review]

Chemotherapeutic wafers for High Grade Glioma

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Editorial group: Cochrane Gynaecological Cancer Group.
Publication status and date: Edited (no change to conclusions), published in Issue 3, 2009.
Review content assessed as up-to-date: 30 July 2008.

Citation: Hart MG, Grant R, Garside R, Rogers G, Somerville M, Stein K. Chemotherapeutic wafers for High Grade Glioma. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD007294. DOI: 10.1002/14651858.CD007294.

ABSTRACT

Background

Standard treatment for high grade glioma (HGG) usually entails biopsy or surgical resection where possible followed by radiotherapy. Systemic chemotherapy is usually only given in selected cases and its use is often limited by side effects. Implanting wafers impregnated with chemotherapy agents into the resection cavity represents a novel means of delivering drugs to the central nervous system (CNS) with fewer side effects. It is not clear how effective this modality is or whether it should be recommended as part of standard care for HGG.

Objectives

To assess whether chemotherapeutic wafers have any advantage over conventional therapy for HGG.

Search strategy

The following databases were searched: The Cochrane Central Register of Controlled Trials (CENTRAL), Issue 2, 2007, MEDLINE, EMBASE, 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 was hand searched from 1999 to 2007, including all conference abstracts. Neuro-oncologists were contacted regarding ongoing and unpublished trials.

Selection criteria

Patients included those of all ages with a presumed diagnosis of malignant glioma from clinical examination and radiology. Interventions included insertion of chemotherapeutic wafers to the resection cavity at either primary surgery or for recurrent disease. Included studies had to be randomised controlled trials (RCTs).

Data collection and analysis

Quality assessment and data extraction were undertaken by two review authors. Outcome measures included survival, time to progression, quality of life (QOL) and adverse events.

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 (hazard ratio (HR) 0.65 confidence interval (CI) 0.48 to 0.86 p = 0.003). In recurrent disease a single RCT was included assessing the effect of Gliadel® and enrolling 222 participants. It did not demonstrate a significant survival increase (HR 0.83 CI 0.62 to 1.10 p = 0.2). There was no suitable data for time to progression or QOL. Adverse events were not more common in either arm, and were presented in a descriptive fashion.

Authors' conclusions

Gliadel® results in a prolongation of survival without an increased incidence of adverse events when used as primary therapy. There is no evidence of enhanced progression free survival (PFS) or QOL. In recurrent disease, Gliadel® does not appear to confer any added benefit. These findings are based on the results of three RCTs with approximately 500 patients in total.

PLAIN LANGUAGE SUMMARY

High grade glioma is a rapidly progressive form of brain tumour: half of all patients will die within a year of diagnosis even after treatment with surgery and radiotherapy

We found two trials, enrolling 272 people with newly diagnosed high grade glioma, which studied the effects of implanting wafers coated with an anti-cancer drug called carmustine (Gliadel®) in the patients' brains once 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 better survival and we found no evidence that carmustine led to a higher risk of side effects.

A similar trial enrolled 222 people who had already been diagnosed with high grade glioma and received surgery but had then had a relapse of disease. In this situation the trial found that carmustine wafers did not prolong the lives of the patients.

BACKGROUND

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 the nerve cells. 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). HGGs belong to grades III or IV and have in common an aggressive and infiltrating nature. The majority of HGGs are Glioblastoma Multiforme (GBM), Anaplastic Astrocytoma (AA) and Anaplastic Oligodendrocytoma (AO). The incidence of HGG is less than 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 2006).

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. Median survival is around one year for GBM, two years for AA and five years for AO (Winger 1989).

Management is based around symptomatic relief and improving survival. The first option is surgery, which is usually required in some form for histological diagnosis. It may be through a biopsy or more aggressive attempted total resection. Currently there is no good evidence from RCTs that either approach results in any difference in survival over best medical care although resection is commonly attempted where feasible (Hart 2000). Radiotherapy is the treatment with most evidence for effectiveness and is now part of standard management, resulting in an increase in median survival from three to four months to around nine to ten months (Walker 1978). The other principle therapy is oral glucocorticosteroids, which have an important role in the reduction of peri-tumoural oedema and can produce a marked improvement in neurological symptoms and survival by themselves (Kaal 2004).

Many trials have been done using various different chemotherapy regimes, the most common being a nitrosurea based regime of Procarbazine, Lomustine 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 QOL.

Recently the oral anti-cancer drug Temozolomide has been approved for use in selected cases of GBM in both the primary and recurrent disease settings. A non-placebo controlled RCT 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 after (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 are including haematological toxicity are not in-frequent and long term effects are unknown.

The most studied type of implantable chemotherapeutic 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 two to three weeks. In theory this should reduce systemic toxicities and allow a greater dose to be provided to residual tumour than PCV chemotherapy (approximately 100 times greater). Wafer implantation at the time of surgery would also simplify subsequent management, as systemic chemotherapy is usually given over a prolonged course of around six months. Early phase II series noted Gliadel® was a safe treatment for use in GBM with associated good survival (Brem 1995; Kleinberg 2004). Despite these proposed advantages it is not clear whether to recommend Gliadel® or any other chemotherapeutic wafer for HGG as either primary therapy or for recurrent disease.

OBJECTIVES

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

- Initial therapy, or;
- Treatment of recurrent disease

METHODS

Criteria for considering studies for this review

Types of studies

RCTs.

Types of participants

Primary therapy: patients of all ages with a presumed diagnosis of HGG on imaging.

Types of interventions

Intervention

- Surgery + chemotherapeutic wafer + radiotherapy

Comparison

- Surgery +/- placebo wafers + radiotherapy +/- systemic chemotherapy e.g. PCV or temozolomide

We included trials which used other forms of supportive care e.g. steroids, anti-epileptic drugs and other drugs as appropriate (Grant 2004) only if similar care was given to both the intervention and comparison group.

Types of outcome measures

Primary outcomes

- Survival: from time of randomisation to death or censoring

Secondary outcomes

- Time to progression (TTP): from time of randomisation to disease recurrence or censoring. Recurrence defined by both clinical and radiological criteria (MacDonald 1990). This is assumed to be roughly synonymous with PFS.
- QOL: as measured by a validated questionnaire.
- Adverse events; nature (as defined using MedDRA® - Medical Dictionary for Regulatory Authorities) criteria and timing. Procedure related mortality defined as within 30 days post-intervention. Specific anticipated adverse events related to the use of wafers include haemorrhage, infection and abscess formation, peri-tumoural oedema, seizures and wound complications.

Search methods for identification of studies

Electronic searches

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. The full search strategy is described in Table 1: an example is given below for brevity. Foreign language journals were eligible for inclusion.

Table 1. Full Search Strategy

Database	Strategy
Medline	MEDLINE (1966 to Jan Week 1 2007) Search Strategy. Terms 1-37, used to identify all randomised and clinical controlled trials were taken from the first two parts of the Highly Sensitive Search Strategy (HSSS) devised by Carol Lefevre. 38. explode "Brain-Neoplasms"/all subheadings 39. explode "Central-Nervous-System-Neoplasms"/all subheadings 40. explode "Cerebral-Cortex"/all subheadings 41. explode "Glioma"/ all subheadings 42. malignant near glioma* 43. glioblastoma* or "glioblastoma multiforme" 44. astrocytoma* or "anaplastic astrocytoma" 45. oligodendrocytoma* or "anaplastic oligodendrocytoma" 46. brain tumo?r* 47. neuroectodermal tumo?r* 48. ependymoma* 49. oligodendroglioma* 50. or/38-49 51. explode "gliadel" 52. explode "carmustine wafers" 53. explode "absorbable implants" 54. explode "drug implants" 55. or/50-54 55. 37 and 50 and 55
Embase	EMBASE (1980 to Jan 2007) Search Strategy. The original search strategy has been adapted from Ovid version to SilverPlatter version, all "MESH" headings were checked in Thesaurus (as the vocabulary was updated in January 2003) and minor changes were made in "MESH" terms. 1.explode "clinical-trial"/all subheadings 2.explode "controlled-study"/all subheadings 3.explode "meta-analysis"/all subheadings 4.explode "crossover-procedure"/all subheadings

Table 1. Full Search Strategy (*Continued*)

	5.explode "double-blind-procedure"/all subheadings 6.explode "single-blind-procedure"/all subheadings 7.explode "randomization"/all subheadings 8.explode "prospective-study"/all subheadings 9.clin* near trial* 10.singl* 11.double* 12.(singl* or double* or trebl* or tripl*) near (blind* or mask*) 13.random* 14.control* 15.#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 16.EC = "HUMAN" 17.#15 and (EC = "HUMAN") 18.explode "brain-tumor"/all subheadings 19.explode "central-nervous-system"/all subheadings 20.explode "brain-cortex"/all subheadings 21.malignant near glioma* 22.glioblastoma multiforme* 23.astrocytoma* or anaplastic astrocytoma* 24.brain tumo?r* 25.neuroectodermal tumo?r* 26.ependymoma* 27.oligodendroglioma* 28.#18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 29. explode"gliadel" 30. explode "carmustine wafers" 31. explode "absorbable implants" 32. explode "drug implants" 33. #29 or #30 or #31 or #32 33. 28 and 33 EMBASE (1980 to Jul 2006) Search Strategy. The original search strategy has been adapted from Ovid version to SilverPlatter version, all "MESH" headings were checked in Thesaurus (as the vocabulary was updated in January 2003) and minor changes were made in "MESH" terms. 1.explode "clinical-trial"/all subheadings 2.explode "controlled-study"/all subheadings 3.explode "meta-analysis"/all subheadings 4.explode "crossover-procedure"/all subheadings 5.explode "double-blind-procedure"/all subheadings 6.explode "single-blind-procedure"/all subheadings 7.explode "randomization"/all subheadings 8.explode "prospective-study"/all subheadings 9.clin* near trial* 10.singl* 11.double*

Table 1. Full Search Strategy (*Continued*)

	12.(singl* or double* or trebl* or tripl*) near (blind* or mask*) 13.random* 14.control* 15.#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 16.EC = "HUMAN" 17.#15 and (EC = "HUMAN") 18.explode "brain-tumor"/all subheadings 19.explode "central-nervous-system"/all subheadings 20.explode "brain-cortex"/all subheadings 21.malignant near glioma* 22.glioblastoma multiforme* 23.astrocytoma* or anaplastic astrocytoma* 24.brain tumo?r* 25.neuroectodermal tumo?r* 26.ependymoma* 27.oligodendroglioma* 28.#18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 29. explode"gliadel" 30. explode "carmustine wafers" 31. explode "absorbable implants" 32. explode "drug implants" 33. #29 or #30 or #31 or #32 33. 28 and 33
Science Citation Index	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" Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library, Internet version, search strategy, Capital letters are MESH terms, the rest are free text terms. The original search strategy was used apart from the term: 18. ((biopsy near versus) near resection)- software did not allow to use this term 1.CENTRAL NERVOUS SYSTEM NEOPLASMS 2.BRAIN NEOPLASMS

Table 1. Full Search Strategy (*Continued*)

	3.GLIOMA 4.(malignant and glioma) 5.(glioblastoma and multiforme) 6.astrocytoma* 7.(anaplastic and astrocytoma*) 8.(brain and tumor*) 9.(neuroectodermal and tumor*) 10.(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9) 11. (gliadel) 12. (carmustine wafers) 13. (absorbable implants) 14. (drug implants) 15. (#11 or #12 or #13) 16. 10 and 15
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
meta-Register of Controlled Trials (mRCT)	meta-Register of Controlled Trials (mRCT): http://www.controlled-trials.com/mrct (Jan 2007) Keywords: brain, glioma, gliadel

The following databases were searched: The Cochrane Central Register of Controlled Trials (CENTRAL), Issue 2, 2007. MEDLINE, EMBASE, SCIENCE CITATION INDEX, Physician Data Query and the meta-Register of Controlled Trials.

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 from 1991 to Jan 2007 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) was contacted regarding any further RCTs involving their product. As they are the sole manufacturer of Gliadel® they would be aware of all research involving their product.

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. 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 authors 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 2 and Table 3. Differences were reconciled by discussion or by consultation with a third review author.

Table 2. 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
Objecive 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	?	Yes

Table 3. External Validity

Criteria	Westphal 2003 & 2006	Valtonen 1997	Brem 1995
Age (mean and range)	Gliadel: 52.6 (21-72). Placebo: 53.6 (30-67)	Gliadel: 55.5 (36-67). Placebo: 53 (36-65).	Gliadel: 48.1 (SD 12.3). Placebo: 47.6 (SD 13.6)

Table 3. External Validity (*Continued*)

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 (60-100). Placebo: 90 (60-100)	Gliadel: 75 (60-100). Placebo: 90 (40-100).	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

- For time to event data (survival and time to progression) we abstracted the HR and its variance from trial reports; if these were not presented, we attempted to abstract the data required to estimate them (Parmar 1998). If it was not possible to estimate the hazard ratio, we planned to abstract the number of patients in each treatment arm who experienced the outcome of interest and the number of participants assessed, in order to estimate a relative risk.

- For dichotomous outcomes (e.g. adverse events) we abstracted the number of patients in each treatment arm who experienced the outcome of interest, in order to estimate a relative risk. For continuous outcomes (e.g. QOL) the final value and standard deviation of the outcome of interest in each treatment arm at the end of follow-up was abstracted for each study. For dichotomous and continuous data, we abstracted the number of patients assessed at endpoint.

- For continuous outcomes (e.g. QOL) the final value and standard deviation of the outcome of interest in each treatment arm at the end of the follow-up was abstracted for each study. For dichotomous and continuous data, we abstracted the number of patients assessed at 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 and integration to RevMan by a single review author.

Assessment of risk of bias in included studies

Appraisal

Any trial deemed relevant was critically appraised using and were allocated to one of three groups, described in Section 6 of the Cochrane Handbook (Higgins 2006) , according to the risk of bias:
Group A - Low risk of bias
Group B - Moderate risk of bias
Group C - High risk of bias
Trials meeting the quality criteria for group A only were included.

Methodological quality of the included trials

Randomisation:

- adequate e.g. a computer-generated random sequence or a table of random numbers (A
- inadequate e.g. date of birth, clinic ID number or surname (B)
- unclear e.g. not reported (C)

Allocation concealment

- adequate e.g. where allocation concealments could not be foretold (A)
- unclear e.g. not reported (B)
- inadequate e.g. the computer generated allocation sequence was displayed so treatment providers could see which arm of the trial the next participant was assigned to, or kept in a sealed opaque envelope (C)
- not used (D)

Blinding of participants, treatment providers and outcome assessors:

- Yes
- No
- Unclear

Loss to follow-up: the number of participants lost to follow up in each intervention arms whose outcomes were not reported at the end of the study was recorded; we also noted if loss to follow-up was not reported.
Any trials meeting the inclusion criteria were critically appraised with tables constructed to summarise internal and external validity (Juni 2001).

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 4.2.
- 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.

Fixed effects models were used for all meta-analyses.
In light of the known benefits of chemotherapy in primary disease, we planned to assign trials including systemic chemotherapy in the control arm to a separate sub-roup and pool results of sub-groups if they showed consistent findings.

If sufficient studies were available, we 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.

RESULTS

Description of studies

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

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.

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 (Valtonen 1997). It included patients (entry criteria aged 18 to 65) who had a good Karnofsky Performance Score (KPS) at baseline (KPS 60 of more). It studied Gliadel wafers or identical placebo wafers not coated in carmustine implanted after resection when GBM was confirmed on frozen section. Further management in both arms included radiotherapy but not systemic chemotherapy. The trial was blinded to participants, treatment providers and outcome assessors. 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 patients from multiple centres through Europe (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

A single trial met the inclusion criteria (Brem 1997). It was set in 27 Neurosurgical centres in the USA and Canada. 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 predefined protocol. The primary outcome was survival; secondary outcome measures included adverse events and mortality.

Excluded studies

We excluded six references for the following reasons:

- A meta-analysis of Gliadel for primary therapy (Mulrow 2003);
- A web based publication for a university technology assessment unit (Brophy 2004);
- 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 retrospective series of the results of Gliadel use in a single institution (Kleinberg 2004).

Risk of bias in included studies

A full analysis of the internal validity of the included studies is presented in Table 2 and summarised below.

Primary gliadel therapy

The design characteristics and internal validity of both trials were similar. Methods of randomisation were not fully described but inclusion/exclusion criteria were and the groups were similar at baseline. Good attention was given to conceal treatment allocation and blind all those involved to treatment groups. The dummy placebo wafer was designed to be identical to Gliadel. Eligibility and ineligibility criteria were clear. Analysis was on an ITT basis, with all patients accounted for and all withdrawals specified. There were no significant methodological differences between the trials to prevent pooling their results in meta-analysis. Therefore both included trials were deemed to be at low risk of bias and eligible for inclusion.

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. 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.

The trial by Westphal 2003 also included 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 application 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. Discrepancy of this kind in the baseline characteristics of treatment groups should be minimised by combination in meta-analysis. The lead pathologists were also blinded to treatment group preventing bias is subsequent treatment.

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 grater 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.

Gliadel for recurrence

Methods of randomisation were not described fully. Good attention was given to blind all those involved in treatment group. The placebo wafer used was identical to Gliadel and this would not have been able to reveal the treatment group a patient was in. Recurrence was defined on radiological criteria alone rather than using more accurate clinical and radiological criteria (MacDonald 1990). 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. 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. 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.

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). Fixed effects models were used as the entry criteria for each study were broadly inclusive. As only two trials were included and both demonstrated a survival benefit individually it was apparent that there was no gross heterogeneity between the trials and a formal statistical test of heterogeneity was deemed unnecessary. No data was included for time to progression or QOL. Adverse events are presented in a descriptive manner due to the low number of events. No study reported any peri-operative mortality. The results for specific adverse events were not statistically more common between arms within each study. Adverse event rates included total event rates of 12/16 (75%) of Gliadel patients and 9/16 (56%) of placebo patients (non-significant) (Valtonen 1997). The rates of neurological complications were not more common in either arm (Westphal 2003).

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 time to progression of QOL. Adverse events included no peri-operative mortality in either arm. There was no statistically significant difference in the rates of the rates of individually specified adverse events. There were 5 cases of infection (Gliadel 4, Placebo 1) and 73 cases of seizures (Gliadel 41, Placebo 32).

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, 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 topical 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 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. Collection of QOL data was poor and lead to the discontinuation of this trial outcome in the largest study. Adverse event rates of Gliadel® were not significantly higher than placebo wafers, although the total number of patients suffering adverse events were incompletely reported in the largest trial. It is not clear whether a wafer itself confers a risk of adverse events above that of standard resection, although an initial phase 1 trials suggested it was well tolerated (Brem 1995).

The inclusion of Grade III tumours in the Gliadel arm, which are a subgroup known to have a better survival than GBM. 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 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.

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 and there was no difference in survival after recurrence between the arms.

The generalisability of the patients and interventions used in the two included studies is summarised in Table 3. 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. In addition, only patients with GBM were studied and not those with other forms of HGG. 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).

AUTHORS' CONCLUSIONS

Implications for practice

There is evidence that Gliadel® increases survival in primary therapy for GBM but not for recurrent disease, and that this benefit is without a significant increase in adverse events. There is no evidence of enhanced 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.

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 tumourogenesis. In all future trials better attention needs to be paid to secondary outcome measures, and entry criteria should be expanded to include a broader range of patients with other forms of HGG. A trial comparing Gliadel with temozolomide is warranted in light of the similar survival benefits in the same patient population.

ACKNOWLEDGEMENTS

Many thanks to the Peninsula Technology Assessment Group (PenTAG, Peninsula Medical School), for allowing use of their report into Gliadel for HGG, on which this review is based. The lead author (MGH) acknowledges the receipt of funding from the Cochrane Gynaecological Cancer Review Group for completion of this review.

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* *Indicates the major publication for the study*

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 (1/3/89-17/1/92). Eligibility criteria: presence of a single unilateral single focus of tumour in the cerebrum showing at least 1.0cm3 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 enrollement. 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 neccessary.
Outcomes	Primary: Survival Secondary: rates of complications, toxicity, quality of life.
Notes	All patients: median survival 31 versus 23 weeks; HR 0.83 CI 0.63-1.10 p=0.19 All patients survival at 6 months: 53% versus 40%, p=0.061 All patients Cox model: HR 0.67 CI 0.51-0.9 p=0.006 GBM subgroup analysis: HR 0.81 p=0.22 GBM subgroup Cox model: HR 0.67 CI 0.48-0.95 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Valtonen 1997

Methods	RCT
Participants	32 consecutive patients from 4 Scandinavian University hospital neurosurgery units (03/1992-03/1993). Inclusion criteria: age 18-65 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 BCNU). Radiotherapy: 'standard' RT (not detailed) was given to both arms post-operatively. Further management

Valtonen 1997 (*Continued*)

	was provided according to need.
Outcomes	Primary: Survival. Secondary: 2 year survival.
Notes	Median survival: Gliadel 58.1 (42-undetermined)versus Placebo 39.9 (37.6-45) weeks Cox model for time from surgery to death for all patients; HR 0.27, CI 0.11-0.68, 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 0.10-0.71, p=0.008 Adverse events: no peri-operative mortality. 21 complications (Gliadel 12, Placebo 9). No quality of life or time to progression data

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Westphal 2003

Methods	RCT
Participants	240 consecutive patients from 38 centres in 14 countries (12/1997-07/1999). Inclusion criteria were: age 18-65 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 BCNU). Radiotherapy: 55-60Gy in 30-33 daily fractions 5 days a week to a focal area with a 2-5 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 surival: Gliadel 13.9 versus Placebo 11.6 months; HR 0.71 CI 0.52-0.96 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 0.45-0.92, p=0.01 GBM only subgroup analysis; median survival Gliadel 13.5 versus Placebo 11.4, HR 0.76, CI 0.55-1.05, p=0.01 Cox model for GBM subgroup; HR 0.69, CI 0.03-0.51, 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

Westphal 2003 (*Continued*)

	Adverse events: no peri-operative mortality. Detailed table of neurological adverse events occurring with a frequency of greater than 5%

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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 0.56-0.95 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 0.57-0.99 p=0.045 GBM subgroup analysis: median survival Gliadel 13.1 versus Placebo 11.4 months, HR 0.78 CI 0.60-1.03 p=0.08 Cox model for GBM subgroup: HR 0.78 CI 0.58-1.05 p=0.1

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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

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

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.

(*Continued*)

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	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 fotemustine, bucladesine wafers, or bucladesine wafers with fotemustine.
Kleinberg 2004	Case series. 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.
Mulrow 2003	This is a meta-analysis of Gliadel therapy presented as Confernce Proceedings. No formal search strategy or systematic review was undertaken.
Sheleg 2002	38 patients with between January 1998 and January 2000.

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 (Random, 95% CI)	0.49 [0.19, 1.23]

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

Review: Chemotherapeutic wafers for High Grade Glioma

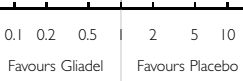
Comparison: 1 Primary Gliadel Therapy

Outcome: 1 Survival

Study or subgroup	log [HR and variance] (SE)	HR and variance IV,Random,95% CI	Weight	HR and variance IV,Random,95% CI
Valtonen 1997	-1.309 (0.4742)		39.3 %	0.27 [0.11, 0.68]
Westphal 2006	-0.3425 (0.1565)		60.7 %	0.71 [0.52, 0.96]
Total (95% CI)			**100.0 %**	**0.49 [0.19, 1.23]**

Heterogeneity: $Tau^2 = 0.34$; $Chi^2 = 3.75$, df = 1 (P = 0.05); $I^2 = 73\%$

Test for overall effect: Z = 1.53 (P = 0.13)

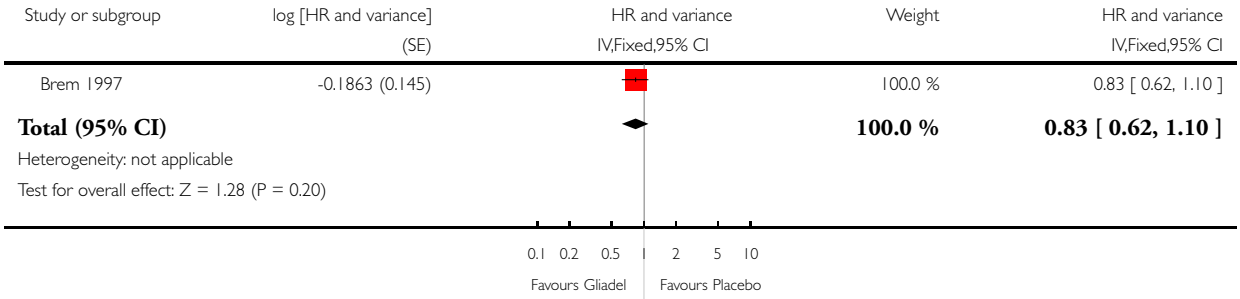


Analysis 2.1. Comparison 2 Gliadel for Recurrence, Outcome 1 Survival.

Review: Chemotherapeutic wafers for High Grade Glioma

Comparison: 2 Gliadel for Recurrence

Outcome: 1 Survival



WHAT'S NEW

Last assessed as up-to-date: 30 July 2008.

8 May 2008	Amended	Converted to new review format.

HISTORY

Review first published: Issue 3, 2008

8 May 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Michael 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.

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.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans