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[Intervention Review]

Biopsy versus resection for high-grade glioma

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ABSTRACT

Background

This is an update of the original review published in the *Cochrane Database of Systematic Reviews* Issue 1, 2000 and updated in 2003, 2007 and 2010.

People with a presumed high-grade glioma (HGG) identified by clinical evaluation and radiological investigation have two initial surgical options: biopsy or resection. In certain situations, such as severe raised intracranial pressure, surgical resection is clinically indicated. Where surgical resection is not feasible, biopsy is the only reasonable option. Most people fall somewhere between these extremes, and in such circumstances it is uncertain which procedure is the best surgical option for the patient. Opinion is divided regarding the relative risks and benefits of each procedure.

Objectives

To estimate the clinical effectiveness of surgical resection compared to biopsy in people with a new presumptive diagnosis of HGG.

Search methods

We updated our searches of the following databases to 12 September 2018: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase. We also handsearched the *Journal of Neuro-Oncology* and *Neuro-Oncology* from 2010 to 2018 (including all conference abstracts).

Selection criteria

We included randomised controlled trials (RCTs) involving people of all ages with a presumed diagnosis of HGG based upon clinical and radiological investigation. Interventions included any form of biopsy or resection. Surgery was at the time of initial presentation and not for recurrence.

Data collection and analysis

Two reviews authors independently assessed the search results for relevance and undertook critical appraisal according to prespecified guidelines. Outcome measures included survival, time to progression/progression-free survival, quality of life, symptom control, adverse events, and mortality.

Main results

We identified a single RCT of biopsy versus resection in presumed HGG. No other articles met the inclusion criteria. Personal communication revealed that an RCT of biopsy versus resection in elderly people with HGG is underway. Further communication as part of this 2018 update revealed that the results of this study are due to be published in 2019.

Biopsy versus resection for high-grade glioma (Review)

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Authors' conclusions

There is no high-quality evidence on biopsy versus resection for HGG that can be used to guide management. The single included RCT was of inadequate methodology to reach reliable conclusions. Further large, multicentred RCTs are required to conclusively answer the question of whether biopsy or resection is the best initial surgical management for HGG.

PLAIN LANGUAGE SUMMARY**Biopsy versus resection for high-grade glioma**

Malignant gliomas are aggressive tumours of the nervous system. Resection (surgery to remove the tumour) may relieve symptoms, but it is uncertain whether it extends survival. Biopsy can confirm diagnosis and carries fewer risks, but it will not extend survival or improve symptoms. Which procedure is the best management option is controversial. We found one small trial looking at this issue, but it proved inadequate and of low quality, and therefore could not answer the question conclusively. Larger, well-designed trials are required in the future.

BACKGROUND

Description of the condition

Gliomas are tumours of the brain and spinal cord, so called because they develop from the glial cells that surround neurons. Gliomas are graded histologically according to the World Health Organization (WHO) classification on a scale of I to IV ([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 subtype glioblastoma multiforme (GBM), anaplastic astrocytoma (AA), or anaplastic oligodendrocytoma (AO).

High-grade gliomas are the most common primary nervous system tumours, with an annual incidence of almost 10 per 100,000 ([Counsell 1998](#)). The peak age of onset is between 50 and 60 years, and generally the clinical presentation is of short duration. Symptoms most commonly include a mixture of headache, focal neurology, and non-specific changes such as altered mental state or gait dysfunction ([Grant 2004](#)).

The natural history is a progressive decline in neurological function, with a median survival of around a year based on selected patients enrolled in clinical trials, although there is not a recent prospective cohort study. Young age, lower histological grade of tumour, and good neurological function at diagnosis are the most reliable clinical prognostic factors. Algorithms can identify patient subgroups with median survival ranging from around a month to greater than three years ([Curran 1993](#); [Lamborn 2004](#)). Curative therapy is rarely possible, necessitating that current therapies should emphasise symptomatic improvement and quality of life. Glucocorticosteroids constitute a fundamental, predominantly symptomatic, component of management. Radiotherapy and chemotherapy are the core therapeutic modalities, both of which have a substantial evidence basis ([Grant 2004](#)).

Description of the intervention

Surgery of various forms has a traditional role in the management of HGG. Biopsy seeks to achieve a histological diagnosis with minimal risk which can be used to guide further therapy; resection aims to remove the majority of tumour with subsequent symptomatic relief and increased survival. It is hypothesised that resection provides a distinct clinical advantage over sole histological confirmation provided by biopsy, and that the risks associated with resection do not offset any possible benefits.

Why it is important to do this review

There is an extensive and conflicting literature on the relative merits of each procedure ([Proescholdt 2005](#); [Schiff 2003](#); [Taylor 2004](#)). Studies are often retrospective case series, whilst direct comparisons are compounded by differences in patient characteristics, surgical technique, and outcome reporting. It is not clear whether the more invasive procedure of resection confers any practical benefits other than histology. The size of any benefit for resection must be quantified along with the risks involved in order to help make informed management decisions.

OBJECTIVES

To estimate the clinical effectiveness of surgical resection compared to biopsy in people with a new presumptive diagnosis of HGG.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) meeting the selection criteria (described in detail below). External signs of each surgical technique are different and often clinically obvious, meaning that blinding is often not feasible and was therefore not an inclusion criterion. We included only studies where the original decision was to randomise people to resection or biopsy; studies that randomised participants to receive another treatment regimen (e.g. radiotherapy, chemotherapy, or 5-aminolevulinic acid (5-ALA)) and subsequently stratified people (in a non-random fashion) according to degree of surgery were not accepted. Foreign language journals were eligible for inclusion.

Types of participants

We included people with a presumed HGG from clinical examination and imaging (computed tomography (CT) or magnetic resonance imaging (MRI), or both). Additional imaging modalities (e.g. positron emission tomography or magnetic resonance spectroscopy) were not mandatory. People were be 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) or WHO score ([Karnofsky 1948](#); [WHO 1982](#)).

Types of interventions

- Biopsy: this included all procedures where the sole primary aim was to sample the tumour for diagnostic purposes. Eligible variations included: freehand or stereotactic guided; frame-based or frameless stereotaxy; CT, MRI, or other imaging (e.g. positron emission tomography or magnetic resonance spectroscopy) as the guiding modality for the neuronavigation system; Stealth, Brainlab, or other commercial manufacturers' equipment; and awake or general anaesthesia. Treatment cross-over was allowed, although ideally minimised in trial design.
- Resection: this included all procedures where the preoperative aim was to remove more tumour than is necessary for diagnosis. Resection is often graded as either attempted total, partial, or palliative debulking, all of which were eligible for inclusion. Assessment of complete resection could be by the surgeons operating opinion but ideally by early postoperative imaging ([Hensen 2008](#)). All aids to achieving surgical resection - including neuro-navigation, 5-ALA/Gliolan-guided resection, Sonowand, and intraoperative MRI - were 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](#); [Nazzaro 1990](#)).
- Postoperative management: in light of the known effectiveness of certain treatments, a management algorithm, ideally conforming to known standards, was desirable ([Grant 2004](#); [Rampling 2005](#)). Medical management of seizures and other symptoms; glucocorticosteroids for brain oedema, symptoms of raised intracranial pressure, or focal deficits; and radiotherapy according to accepted guidelines were ideally included. Chemotherapy (procarbazine, lomustine (CCNU), and vincristine (PCV), temozolomide, or other) in either arm was left to the discretion of the individual attending physician.

Types of outcome measures

Primary outcomes

- Survival: this was time (usually in days or months) with confidence intervals (CI) and a hazard ratio (HR) with variance displayed using a Kaplan-Meier plot.

Secondary outcomes

- Time to progression/progression-free survival: open and thorough criteria should have been used to define recurrence according to clinical symptoms, imaging, or increasing steroid therapy (Wen 2010).
- Quality of life: a reliable and objective grading measure should have been used, e.g. the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire/Brain Cancer module (EORTC QLQ-C30/BN-20) and Functional Assessment of Cancer Therapy (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 (MedRa 2008). Examples include: haematoma, wound complications, infection (and site), cerebrospinal fluid leak, oedema, seizures, and general medical complications. Further procedures required for complications should have been noted. Both the total number of complications and complications per participant should have been stated.
- Mortality: cause-specific immediately following the procedure and at 30 days.

Ideally all outcome measures should have been assessed at frequent intervals by at least two assessors acting independently.

Search methods for identification of studies

Electronic searches

For this update we searched the following databases up to 12 September 2018:

- the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 8), in the Cochrane Library;
- MEDLINE via Ovid (2010 to August week 5 2018);
- Embase via Ovid (2010 to 2018 week 37).

The search strategies are presented in the [Appendices](#).

Searching other resources

We searched the references of all identified studies for additional trials.

Handsearching

We updated the handsearch of the *Journal of Neuro-Oncology* and *Neuro-Oncology* from 2010 to September 2018 in order to identify trials that may not have been present in the electronic databases. This included searching all conference abstracts published in the journals.

Personal communication

For the 2007 update, we contacted the following individuals by email for information on any current or pending RCTs: MJ van den

Bent, M Fabbro, K Hopkins, F Laigle, D Netuka, A Obwegeser, G Pesce, M Weller, W Wick, J Wolff.

For the 2010 update, we contacted the following individuals by email for information on any current or pending RCTs: M Weller, W Wick, S Short, R Stupp.

For the 2019 update, we contacted Khe Hoang Xuan to obtain information on the ANOCEF study, which is due to be presented either at the American Society of Clinical Oncology (ASCO) (June 2019) or European Association of Neuro-Oncology (EANO) (September 2019) conference later this year.

Data collection and analysis

Selection of studies

We conducted identification of studies in two stages. Two review authors (MGH/RG up to 2010 and GG/ES up to 2018) independently examined abstracts returned by the original search and screened them to determine if they met inclusion or exclusion criteria. Next, full texts of the selected reviews were obtained, which were further examined and compared with the inclusion and exclusion criteria. Any disagreements were resolved through discussion. If sufficient data were not available for assessment, then the authors of the relevant trial were contacted.

Data extraction and management

Two review authors (MGH and RG) independently abstracted from the included studies data on characteristics of participants, interventions, study quality, endpoints, and deviations from protocol using a form prespecified to obtain the information required for a 'Characteristics of included studies' table ([Table 1](#); [Table 2](#)). Any differences were reconciled by discussion or by consultation with a third review author (MGH and RG).

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 Centre for Reviews and Dissemination (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 for Systematic Reviews of Interventions* (Higgins 2009). Critical appraisal was performed independently by two review authors (MGH and RG). Any disputes were resolved through discussion.

Measures of treatment effect

- Time-to-event data (survival and time to progression/progression-free survival): the HR and its variance were abstracted.
- Continuous outcomes (quality of life and symptoms): the final value and standard deviation of the outcome of interest in each treatment arm at the end of the follow-up was abstracted.
- Dichotomous outcomes (adverse events and mortality): the number of people in each treatment arm who experienced the outcome of interest was abstracted in order to estimate a relative risk (RR).
- For continuous and dichotomous data, we abstracted the number of people assessed at endpoints.

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, we contacted the study authors.

Assessment of heterogeneity

We would have used visual inspection of forest plots in combination with the χ^2 test to gauge whether trials were of sufficient homogeneity to be combined in meta-analysis.

Assessment of reporting biases

We planned to construct a funnel graph of trial effect versus trial size with the data from all included studies entered in order to investigate the likelihood of publication bias.

Data synthesis

A single review author (MGH up to 2010 and GG up to 2018) performed integration of data into [Review Manager 5](#).

- Time-to-event data: HR and variance were pooled using the generic inverse-variance function of Review Manager 5.
- Continuous outcomes: we pooled the weighted mean differences between the treatment arms at the end of the follow-up using the mean difference (MD) method if all trials measured the outcome on the same scale, or the standardised mean difference (SMD) method otherwise.
- Dichotomous outcomes: the RR for each study was calculated and then all studies were pooled.

We used random-effects models for all meta-analyses ([DerSimonian 1986](#)).

Subgroup analysis and investigation of heterogeneity

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

We proposed a funnel plot with the data from all included studies if sufficient studies were identified in order to investigate the likelihood of publication bias.

Sensitivity analysis

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

RESULTS

Description of studies

Results of the search

The original electronic database searches yielded a total of 2100 citations, as follows.

- MEDLINE: 177
- CCTR: 51

- CCN (Specialised Register of Trials): 300
- CANCERLIT: 133
- Embase: 743
- BIOSIS: 370
- Science Citation Index: 326

Reference list checking, handsearching, and personal communication failed to reveal any additional relevant trials.

Updates

The update in February 2003 revealed an additional 271 references from MEDLINE; 44 references from Embase; and one reference from CENTRAL. Three studies for potential inclusion were identified, of which two were excluded. The second update in January 2007 identified no further RCTs for inclusion.

The update in November 2010 revealed an additional 606 references from MEDLINE; 765 references from Embase; and 122 references from CENTRAL, for the period 2006 to 2010. No further RCTs were selected for inclusion.

The update in December 2016 revealed an additional 1363 references from MEDLINE; 2014 references from Embase; and 1358 references from CENTRAL, for the period 2010 to 2016. No further RCTs were selected for inclusion.

The update in September 2018 revealed an additional 302 references from MEDLINE; 220 references from Embase; and 1258 references from CENTRAL, for the period 2016 to 2018. No further RCTs were selected for inclusion.

Included studies

We identified one RCT of biopsy or resection for HGG ([Vuorinen 2003](#)), which was evaluating biopsy versus debulking in people over 65 years old. The study was conducted in a single institution based in Finland, recruiting between 1993 and 1996. A full analysis of its design is presented in the [Characteristics of included studies](#) and [Table 3](#).

Excluded studies

We identified but then excluded 17 other studies ([Characteristics of excluded studies](#)). Three studies were literature reviews rather than RCTs ([Proescholdt 2005](#); [Quigley 1991](#); [Taylor 2004](#)). A single study was a meta-analysis ([Tsitladikis 2010](#)). Three studies were prospective but assessed symptoms only ([Fadul 1988](#); [Sawaya 1998](#); [Whittle 1998](#)). Another study was a series of three RCTs, however the participants were not randomised to biopsy or resection, but rather to different radio-chemotherapy regimens, and were subsequently analysed post hoc according to the extent of tumour resection ([Simpson 1993](#)). Six other reports of RCTs assessed neurosurgical aids to gross total resection in HGG, but they did not directly compare biopsy versus resection: three were on fluorescence-guided surgery ([Eljamel 2008](#); [Stummer 2006](#); [Stummer 2008](#)), two on neuro-navigation ([Willems 2006](#); [Wu 2007](#)); and one on awake cortical mapping ([Gupta 2007](#)). The other four RCTs considered adjuncts to resection rather than biopsy versus resection, namely the application of chemotherapy wafers to the resection cavity ([Brem 1995](#); [Valtonen 1997](#); [Westphal 2003](#); [Westphal 2006](#)), which is the subject of another Cochrane Review ([Hart 2007](#)).

Ongoing studies

An RCT of biopsy versus resection in elderly people with HGG is ongoing in France under ANOCEF, and updated personal communication has revealed that the results of this trial are expected to be presented in mid-2019 at ASCO or EANO annual meetings.

A protocol for an RCT was developed by the NCRI Brain Tumour Group in the UK at the time of the 2010 update, but unfortunately this trial did not attract sufficient funding to commence.

Risk of bias in included studies

Full analyses of the internal and external validity of this study are provided in [Table 1](#) and [Table 2](#).

- Power: the authors did not provide a sample size calculation based on the primary endpoint of survival. If we assume an optimistic median survival of 100 days in the biopsy arm (in the trial the actual survival was 85 days) and estimate the number of people in each arm required to show a conservative increase in survival of 30 days in the resection arm (145 days in the trial) with a power of 80%, an accrual period of two years, and follow-up period of two years, a trial of approximately 500 people (250 in each arm) would be required.
- Allocation: the method of randomisation and its concealment was not described. No stratification for age, tumour grade, or performance status was performed at randomisation. It is unclear if all potentially eligible people were approached for participation and whether the results reflect a continuous series of participants or a selected series.
- Baseline participant characteristics: there were inequalities between the two study arms at baseline;
 - * 85% of people in the biopsy arm were 70 years or over compared with 50% in the resection arm;
 - * 23% of people in the biopsy arm had a KPS greater than or equal to 80 compared with 60% in the resection arm;
 - * 77% of people in the biopsy arm received radiation therapy compared with 90% in the resection arm.
- Blinding: investigators and participants were not blinded to study arm allocation. Although initial blinding to study arm is impossible for the attending surgeon and unlikely to be reliable for the participant, investigators at follow-up could potentially be blinded, as the larger cosmetic defect produced by a craniotomy (required for resection) is not always immediately obvious, particularly to physicians.
- Outcome detection: the lack of blinding and single objective outcome measure applied (survival) creates the potential for bias in the reporting of results. Time to deterioration as defined here will depend on the social support systems available to each participant in determining the detection accuracy.
- Selective reporting: no intention-to-treat analysis was performed. The seven people who were randomised but later excluded were not analysed as part of the trial results. Data on only 13 of 16 people in the biopsy arm (81%) and 10 of 14 people in the resection arm (71%) were provided.
- Postoperative management: the lack of blinding is of significant concern here, and the actual treatments are not clearly specified. Time to deterioration did not differ between study arms, which could be consistent with more aggressive management of the resection group at recurrence (e.g. further

surgery or chemotherapy). The lower percentage of people receiving postoperative radiotherapy after biopsy as opposed to resection was accounted for by poor patient status, but the lack of blinding could have introduced treatment bias into the equation.

- Statistics: all statistical tests appeared to be appropriate, but no confidence intervals were given for time to deterioration.

Effects of interventions

Primary outcome measures

In light of there being only a single trial suitable for inclusion, no meta-analysis was performed, and instead a description of outcome measures reported in the trial is provided.

Survival was recorded from the time of surgery for the valid study group (i.e. not intention-to-treat analysis); this was demonstrated in a Kaplan-Meier plot and compared by non-parametric log rank Chi² test. Median survival times were: biopsy 85 days (95% confidence interval (CI) 55 to 157) versus resection 171 days (95% CI 146 to 278) (P = 0.0346). The hazard ratio (HR) adjusted for tumour grade was 2.621 (95% CI 1.035 to 6.641) (P = 0.0422). The HR adjusted for radiotherapy dose was 2.729 (95% CI 1.035 to 7.195) (P = 0.0423).

Secondary outcome measures

Time to deterioration (defined as "not able to live at home; time after which patient stayed permanently in a nursing home") was 72 days in the biopsy group and 105 days in the resection group (no 95% CI given) (P = 0.056). No quality of life data were recorded. No participant in the biopsy group had a procedure-related complication, however one of the 10 people in the resection group had a postoperative haematoma that required reoperation. Of note, this participant had a decline in their KPS postoperatively from 80 to 50. No other adverse events were documented.

DISCUSSION

There is an extensive literature on surgery for HGG, and comprehensive reviews of this have been published ([Proescholdt 2005](#); [Taylor 2004](#)). The majority of studies are non-randomised, highly selected, and retrospective. The limitation of non-randomised studies is the inherent risk of bias in allocating people to a treatment in day-to-day practice: 'fitter' people receive resection, whilst 'inoperable' tumours are subject to biopsy. Preoperative prognostic factors including age, performance status, and histology are known to be the most significant determinants of outcome ([Curran 1993](#); [Lamborn 2004](#)). This obstacle essentially nullifies any robust conclusions that can be made from studies of the above design. To enable objective scientific comparison, an equal and consecutive series of people must be randomly allocated to either treatment.

Our literature search identified only one RCT that met our inclusion criteria ([Vuorinen 2003](#)). Due to underpowering and methodological limitations, the findings are tainted by a high likelihood of being affected by bias and chance. Although the authors reported their findings as being in favour of resection, a technically more correct description would be that the findings from this trial are of insufficient reliability to be used to influence treatment decisions. The included study should be viewed as

evidence that RCTs are feasible in the area and used as a building block for further RCTs.

Compelling results for extent of resection having a positive correlation with survival are presented in a post hoc analysis of 243 people evaluated in a trial of 5-ALA (Stummer 2008). In this study people were randomised to resection of a newly diagnosed HGG by either white light or fluorescence-guided resection (with oral 5-ALA). Re-stratification into groups that received complete versus incomplete resection revealed a survival benefit in favour of complete resection (HR 0.54, 95% CI 0.41 to 0.71). Despite these favourable results, this report still does not represent an RCT with the primary goal of comparing biopsy with resection, and was therefore ineligible for inclusion in this review.

When a patient presents with clinical features suggestive of a HGG, imaging is accurate with regards to the diagnosis of a tumour, but it is not accurate for the identification of the grade of tumour (Kondziolka 1993; Murphy 2002). A pathological diagnosis is desirable to allow identification of other treatable conditions such as cerebral abscess, and to permit identification of tumours with specific treatments such as germinomas. In the included RCT (Vuorinen 2003), the initial imaging diagnosis was found to be inaccurate in 21% (6 out of 29 cases), with 50% of inaccurate diagnoses being for non-malignant conditions. Brain tumours are often heterogenous, and it is possible that small tissue samples through a biopsy may not be diagnostic or representative of the tumour as a whole. One prospective series of people who underwent biopsy then resection a mean of three weeks later, found that biopsy correctly guided therapy in 91% of cases (Woodworth 2005). Biopsy of a small area of anaplasia in a predominant low-grade glioma may lead to inappropriately early therapy. Conversely, biopsy sampling of a small area of more benign-looking tissue in a HGG may lead to a delay in treatment. Within clinical trials, this may lead to some people with low-grade glioma being included in the biopsy arm, who would have a reasonable prospect of long-term survival.

With the lack of primary outcome data, careful attention needs to be paid to the risks of each patient to assess the cost-benefit ratio. Biopsy is considered to be a low-risk procedure, with a morbidity rate from retrospective series of around 3.5% and a mortality rate of less than 1% (Hall 1998). Practically, biopsy can be performed under local anaesthesia and as a day-case procedure. The results of prospective studies of complications following neurosurgery in brain tumours are summarised in Table 4. In two prospective series, resection had a morbidity rate of 32% and a mortality of 1.7% to 3.3% (Fadul 1988; Sawaya 1998). In eloquent areas of the brain, surgery still carries a low risk of morbidity and can improve dysphasia when intraoperative brain mapping and awake craniotomy is utilised (Whittle 1998). Regarding relief of symptoms from resection, there is some evidence that 32% will improve, while in 58% to 76% of cases this was not discernibly different (Fadul 1988; Sawaya 1998). However, while surgery can improve some symptoms, it can also create new postoperative deficits.

Only broad guidelines can be made from our findings, and treatments must be considered on an individual basis. Biopsy may be the only option for certain deep-seated tumours (e.g. infiltrating the thalamus, corpus callosum, or brainstem), while small, superficially placed frontal tumours can often be resected

with a low risk of new deficits. Due to the associated risks of resection, biopsy is currently preferred for people with poor performance status, of older age, or when the lesion is in an anatomically prohibitive location for resection (e.g. in deep or eloquent regions). In other selected groups of people the risks of resection may be lower, and there may be a greater likelihood for benefits from surgery. In some people the prognosis may be deemed so poor that treatment would only be palliative, and histology would not affect this management direction.

Histological diagnosis is desirable for the management of a suspected brain tumour, and can be achieved either through biopsy or resection. There is no good evidence from RCTs that resection offers any clear advantage over biopsy. Stereotactic biopsy has a low risk of complications and is an effective tool for histology, although there is a risk of sampling error. However, biopsy is not risk-free and has no direct therapeutic action. For each patient the relative benefits and risks of each procedure need to be considered. Future trials in this area need to be larger and randomised, with greater attention to symptom profile and quality of life in their outcome analysis.

AUTHORS' CONCLUSIONS

Implications for practice

No evidence-based recommendations as to the best surgical management of people with high-grade glioma can be made.

Until there is better evidence, it is important to consider each case individually and for the surgeon to carry out the procedure which is deemed to be the most appropriate for that particular patient, taking into account the risks and benefits. Such decisions are best made at a multidisciplinary team meeting (NICE 2007).

Given the lack of randomised controlled trial-based evidence, individual clinicians should be encouraged to enter their patients into a controlled clinical trial, if such a trial were to be established in the future.

Implications for research

In this highly controversial area, for both optimum patient care and health economics, it is imperative to conduct high-quality, large-scale randomised controlled trials of biopsy versus resection for high-grade glioma.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Vuorinen 2003

Methods	Randomised controlled trial
Participants	30 patients were enrolled from a single university hospital between 1993 to 1996. Inclusion criteria were radiologically malignant supratentorial glioma, Karnofsky Performance Status greater than or equal to 60 (error in the methods section of the paper, where as it states greater than 60), patients older than 65 years of age, informed consent to participate in the study. Symptoms/evidence of raised intracranial pressure was not an exclusion criterion. No stratification for age or performance status.
Interventions	Stereotactic biopsy versus open craniotomy and resection. A pre-randomisation brain scan (CT or MRI) was performed. Procedures were performed by an experienced neurosurgeon. An estimate of extent of resection was made from a postoperative brain scan in those undergoing resection between days 1 and 3. Clinical evaluation was performed 1 week after surgery, and Karnofsky Performance Score was evaluated.
Outcomes	Primary: survival. Secondary: time to deterioration, quality of life, morbidity and mortality. Statistical tests were: non-parametric Kaplan-Meier method compared non-parametric log rank Chi ² test.
Notes	4 exclusions from resection group (1 withdrew consent, 1 each of lymphoma, haematoma, and infarct) and 3 exclusions from the biopsy group (2 metastases and 1 haematoma). No intention-to-treat analysis. Total resection rate was 20%.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Data awaited from author.

Vuorinen 2003 (Continued)

Allocation concealment (selection bias)	High risk	The signs associated with a craniotomy and resection of a tumour would be difficult to disguise.
Blinding (performance bias and detection bias) All outcomes	High risk	The signs associated with a craniotomy and resection of a tumour would be difficult to disguise.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All prespecified outcome criteria had 100% completion for the treatment groups, but this was not an intention-to-treat analysis.
Selective reporting (reporting bias)	Unclear risk	No intention-to-treat analysis; 7 participants excluded from final analysis
Other bias	Low risk	No industry sponsorship declared.

CT: computed tomography

MRI: magnetic resonance imaging

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Brem 1995	An RCT comparing Gliadel with placebo wafers in recurrent HGG (analysed in detail in Hart 2007)
Eljamel 2008	A small, single-centre RCT of 27 participants comparing fluorescence-guided surgery and photodynamic therapy (ALA and Photofrin) in glioblastoma multiforme. There is no reporting of extent of resection in relation to survival.
Fadul 1988	Prospective study of surgery for HGG but considering primarily morbidity and mortality only. This study forms part of the morbidity analysis of craniotomy versus biopsy described in the Discussion .
Gupta 2007	An RCT of 53 participants comparing awake craniotomy versus general anaesthesia for intrinsic lesions of eloquent cortex. No analysis of extent of resection in relation to survival.
Proescholdt 2005	A systematic review evaluating the level of evidence and methodological aspects of studies reporting on the extent of resection for brain tumours.
Quigley 1991	Literature review, not RCT
Sawaya 1998	Prospective study of surgery for brain tumours considering primarily morbidity and mortality only. This study forms part of the morbidity analysis of craniotomy versus biopsy described in the Discussion .
Simpson 1993	Meta-analysis and prognostic factor determination from 3 radio-chemotherapy trials
Stummer 2006	<p>RCT considering fluorescent-guided surgery compared to normal resection.</p> <p>322 participants aged 23 to 73 years were enrolled. Fluorescence-guided surgery resulted in an increase in complete resections (65% versus 36%) and a higher 6-month progression-free survival (41% versus 20%). No effect was noted on survival. Adverse effects were reported as unchanged.</p> <p>Some questions remain about the methods used in this trial. In brief, there was a high exclusion rate, and some concern over why some participants in the treatment arm dropped out before radiotherapy. Definitions of the 2 main outcome measures of complete resection and recurrence are also not robust or stringent enough for clinical use. External validity is low, with the participants very highly selected and not reflecting those in routine clinical practice. Finally, there is some con-</p>

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Study	Reason for exclusion
	cern that the more aggressive resections in the treatment arm resulted in greater postoperative morbidity, however not enough detail is provided to fully analyse this area.
Stummer 2008	This is a follow-on post hoc re-stratification analysis of Stummer 2006 that randomised participants to primarily white light or fluorescent-guided surgery.
Taylor 2004	This is a systematic review and descriptive analysis of studies examining the role of surgery for malignant glioma; no meta-analysis was performed. There is a detailed and thoughtful description of many historical references regarding extent of resection in HGG.
Tsitladikis 2010	A semi-objective systematic review and meta-analysis focused on the same subject as this Cochrane Review. Literature search strategy and study methods are incompletely reported. Study appraisal and insight is limited. Inclusion of a majority of retrospective studies into the analysis is of dubious scientific merit (see Discussion).
Valtonen 1997	An RCT of Gliadel wafers versus placebo after resection for newly diagnosed HGG (analysed in detail in Hart 2007)
Westphal 2003	An RCT of Gliadel wafers versus placebo after resection for newly diagnosed HGG (analysed in detail in Hart 2007)
Westphal 2006	This is long-term follow-up of Westphal 2003 (analysed in detail in Hart 2007).
Whittle 1998	Prospective series of 40 participants presenting left-sided hemispheric lesions with and without dysphasia undergoing awake craniotomy. This study forms part of the morbidity analysis of craniotomy versus biopsy described in the Discussion .
Willems 2006	<p>An RCT of neuro-navigation-aided resection compared with normal resection.</p> <p>A total of 45 participants were recruited, and the results are part of a preliminary analysis of a larger study. There was no difference in the primary outcomes of survival or extent of resection. The surgeon felt that neuro-navigation was useful, and it did not lead to considerably longer operating times or greater adverse events. It is suggested that there were fewer acute deficits in the first few days postoperatively in the neuro-navigation arm, and that the treatment arm had a lower use of steroids.</p> <p>The main flaws with regard to this study were that its participants were highly selected, and possibly that the non-treatment arm had a slightly better prognosis at baseline. This fact and the coincidental early deaths of 3 participants in the treatment arm, together with the low power to detect effects, put the trial at a significant risk of a type 1 error.</p>
Wu 2007	This is an RCT of diffusion tensor imaging-based functional neuro-navigation for gliomas of the pyramidal tracts. While the study arm for the HGG subgroup was reported to have a higher percentage of gross total resection and longer survival, a post hoc re-stratification analysis, similar to that reported by Stummer 2008 , was not performed.

ALA: aminolevulinic acid
HGG: high-grade glioma
RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Biopsy versus resection for high-grade glioma

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival	1	23	Hazard Ratio (Random, 95% CI)	2.62 [1.03, 6.64]

Analysis 1.1. Comparison 1 Biopsy versus resection for high-grade glioma, Outcome 1 Survival.

ADDITIONAL TABLES

Table 1. Internal validity

Characteristic	Study (Vuorinen 2003)
Power calculation?	No
Proper randomisation?	Not stated (awaiting author feedback)
Groups similar at baseline?	Unclear. KPS 78 in resection group and 70 in biopsy group (no statistical test used). Unequal gender distribution
Blinding	Not for investigators or participants
Eligibility criteria stated?	Yes
Objective outcome measures?	Only survival. All other measures were subjective
Analysis on ITT basis?	No
All participants accounted for?	Not stated. Unclear if it is a consecutive series
Withdrawals specified?	At least 7 withdrawals were not included in ITT analysis
Withdrawal reasons given?	Yes
Conflict of interest?	No industry sponsorship or other conflict declared

ITT: intention-to-treat

KPS: Karnofsky Performance Score

Table 2. External validity

Study	Sample size	Age (median and range)	Sex (%M:F)	Histology	KPS	Extent of surgery	Subgroups analysed	Follow-up
Vuorinen 2003	Total = 30 Resection = 14 Biopsy = 16	Resection: 70 (66 to 80). Biopsy: 72 (67 to 79)	Resection: 7 male and 3 female. Biopsy: 4 male and 9 female	Resection: grade IV: 10; malignant lymphoma: 1; haematoma: 1; infarct: 1; withdrawal: 1. Biopsy: grade IV: 8; grade III: 5; metastases: 2; haematoma: 1	Resection: 80 (60 to 90). Biopsy: 70 (60 to 90)	Total: 2; Subtotal: 7; Resection: 1	None. Subsequent hazard ratios stratified for tumour grade and radiotherapy dose.	Up to 590 days

KPS: Karnofsky Performance Score

Table 3. Design characteristics

Study	Setting	Age	Inclusion criteria	Exclusion criteria	Treatment regimen	Outcome measures
Vuorinen 2003	A single university teaching hospital in Finland	65 years or older	<ul style="list-style-type: none"> • Radiologically malignant supra-tentorial glioma • KPS greater than 60 at time of randomisation • Patient older than 65 years at time of randomisation • Informed consent to participate in the study 	"Patients who did not fit the inclusion criteria or were unwilling to participate"	Radiotherapy, details not specified. No explicit postintervention management guidelines or protocol.	<ul style="list-style-type: none"> • Survival • Time of deterioration (defined as not able to live at home; time after which participant stayed permanently in hospital or in nursing home) • Postoperative complications

KPS: Karnofsky Performance Score

Table 4. Complications following neurosurgery for brain tumours

Study	Numbers	Mortality	Morbidity	Haematoma	Abscess	Seizure
Vuorinen 2003	30	0%	3.3%	3.3%	0%	0%
Taylor 1999	200	1%	16.5%	1.5%	-	-
Sawaya 1988	327	1.7%	32%	0.5%	1.5%	2.5%
Fadul 1988	104	3.3%	31.7%	-	-	-

APPENDICES

Appendix 1. CENTRAL search strategy (2010 update onwards)

- #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)

Appendix 2. MEDLINE search strategy (2010 update onwards)

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

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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

Appendix 3. Embase search strategy (2010 update onwards)

- 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

key:

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

Appendix 4. MEDLINE search strategy (original)

1966 to Jan Week 1 2007

The original search strategy has been adapted from the Ovid version to the Silver Platter version. Terms 1-37, used to identify all randomized and clinical controlled trials were taken from the first two parts of the Highly Sensitive Search Strategy (HSSS) devised by Carol Lefebvre.

- 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 brain tumor?r*
- 46 neuroectodermal tumor?r*
- 47 ependymoma*
- 48 oligodendroglioma*
- 49 or/38-48
- 50 explode "Biopsy"/ all subheadings
- 51 explode "Neurosurgical-Procedures"/ all subheadings

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52 explode "Neurosurgery"/ all subheadings
53 biops* near resect*
54 extent of resection
55 cytotoreduct* near surg*
56 craniotom*
57 or/50-56
58 #47 and #57
59 #37 and #58

Appendix 5. CANCERLIT search strategy (original)

1983 to February 2003

This database was searched using the same strategy as that used for Medline.

Appendix 6. BIOSIS Previews search strategy (original)

1985 to 2000

Words or phrases in the Title, Subjects or Abstract were searched.

1. randomi?ed & contol* & trial
2. control* & clinical & trial
3. random* & allocat*
4. double & (blind* , mask*)
5. single & (blind* , mask*)
6. clinical & trial
7. control & group
8. control* & trial
9. clinical & study
10. control* & study
11. OR/1-10
12. brain & tumo*r
13. brain & neoplasm
14. brain & cancer
15. neuroectodermal & (tumo*r , neoplasm)
16. malignant & glioma
17. glioblastoma , (glioblastoma & multiforme)
18. astrocytoma , (anaplastic & astrocytoma)
19. ependymoma
20. oligodendroglioma
21. tumor [Major Concept]
22. OR/12-21
23. "extent of resection"
24. "biopsy versus resection"
25. biopsy & resection
26. stereota* & biopsy
27. combined & modality & therapy
28. neurosurg*
29. surg* & treatment
30. OR/23-29
31. 22 AND 30
32. 11 AND 31

Appendix 7. Science Citation Index search strategy (original)

1981 to 2000

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 8. Physician Data Query (PDQ) search strategy (original)

<http://www.nci.nih.gov/cancertopics/pdq>

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

Treatment

Active and closed

Phase III and IV

Appendix 9. meta-Register of Controlled Trials (mRCT) search strategy (original)

<http://www.controlled-trials.com/mrct>

Keywords: brain, biopsy, glioma

WHAT'S NEW

Date	Event	Description
4 June 2019	New citation required but conclusions have not changed	Author list updated.
29 April 2019	New search has been performed	Searches updated to September 2018.

HISTORY

Protocol first published: Issue 1, 2000

Review first published: Issue 1, 2000

Date	Event	Description
11 February 2015	Amended	Contact details updated.
27 March 2014	Amended	Contact details updated.
29 October 2010	New search has been performed	Search strategy amended and updated. No new studies identified. Text revised but conclusions unchanged.
19 August 2008	Amended	Converted to new review format. The introduction, description of studies, methodology and discussion have been modified.
15 April 2007	Amended	Minor update: 15 April 2007. New studies sought but none found: 5 January 2007. New studies found and included or excluded: 4 February 2003. Conclusions changed: 15 April 2007. Reformatted: 15 April 2007.
23 February 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

All authors contributed to this updated version of the review.

DECLARATIONS OF INTEREST

Michael G Hart: None known
Robin Grant: None known
Gareth RL Grant: None known
Emma F Solyom: None known

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None declared.

INDEX TERMS

Medical Subject Headings (MeSH)

*Biopsy; *Brain Neoplasms [pathology] [surgery]; *Glioma [pathology] [surgery]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Aged; Humans; Middle Aged