Biopsy versus resection for high grade glioma (Review)

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TABLE OF CONTENTS

[Intervention Review]

Biopsy versus resection for high grade glioma

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ABSTRACT

Background

Patients with a presumed primary brain tumour from clinical examination and radiological investigation have two initial surgical management options; biopsy or resection. In certain acute situations such as severe raised intracranial pressure, surgical resection is clinically indicated. Where surgical resection is not practical, biopsy is the only reasonable option. Most patients fall somewhere between these extremes, and in these cases it is uncertain which procedure offers 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 patients with a new lesion suspicious of malignant glioma.

Search strategy

The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Cancer Network Register of Trials, MEDLINE, EMBASE,CANCERLIT, BIOSIS and SCIENCE CITATION INDEX. 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 Neuro-oncologists were contacted regarding ongoing and unpublished trials. The search was updated in 2003 and January 2007.

Selection criteria

Patients included those of all ages with a presumed diagnosis of malignant glioma from clinical examination and radiology. Interventions included biopsy or resection of any form. Surgery was at the time of initial presentation and not for recurrence. Included studies have to be RCTs. Outcome measures include survival, time to progression, quality of life (QOL), symptom control, morbidity and mortality.

Data collection and analysis

The search results were assessed for relevance. Critical appraisal and data extraction was undertaken by two authors.

Main results

One RCT of biopsy versus resection in presumed malignant glioma was identified, and it is discussed in this review (Vuorinen 2003). Ten other articles were identified for possible inclusion however all failed to meet selection criteria and were excluded. The hand searching was unproductive, although personal communication revealed an RCT of biopsy versus resection in the elderly with HGG is due to commence in France in early 2007.

Authors' conclusions

There is no high quality evidence with which to base management decisions on. The single RCT for biopsy versus resection in malignant glioma is inadequate to reach conclusions from, due to under-powering and other methodological shortcomings. Further large multi-centred RCTs are required to conclusively answer the question of whether biopsy or resection is superior.

PLAIN LANGUAGE SUMMARY

Malignant gliomas are aggressive tumours of the nervous system, the management of which is usually palliative. Resection may relieve symptoms but there is uncertainty that it extends survival. Biopsy can confirm diagnosis and carries fewer risks, but will not extend survival or improve symptoms. It is controversial as to which procedure is the best management option

One small randomised controlled trial (RCT) addressing this question was found but the trial proved inadequate in design to answer the question conclusively. Larger well designed RCTs are required.

BACKGROUND

Gliomas are tumours of the brain and spinal cord, so called because they develop from the glial cells which form structures that surround the nerve cells. Gliomas are graded in histology by the World Health Organisation (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 Glioblastoma Multiforme, Anaplastic Astrocytoma and Anaplastic Oligodendrocytoma.

HGG 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 short. Symptoms most commonly include a mixture of headache, focal neurology, and non-specific changes, such as altered mental state or gait dysfunction.

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 no recent prospective cohort study. Young age and good neurological function at diagnosis are the most reliable clinical prognostic factors. Simple algorithms can identify patient subgroups with median survivals ranging from around a month to almost five years (Curran 1993; Lamborn 2004). Curative therapy is rarely possible, and current therapies are aimed at palliation. Standard therapy has an evidence basis for glucocorticosteroids, radiotherapy and chemotherapy (Grant 2004).

Surgery has a traditional role in the management of malignant glioma. The first clinical decision is usually whether to pursue with surgery, and if so what type. There are two procedures that are most commonly used, biopsy or resection. Biopsy seeks to achieve a histological diagnosis with minimal risk, while resection aims to provide symptomatic relief and an increase in survival. It is hypothesised that resection provides a distinct clinical advantage over simple histological confirmation and that the risks associated with resection do not offset any possible benefits.

The literature is conflicting on the relative merits of each procedure. 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

The aim of this study is to establish whether if resection holds any advantage over biopsy for HGG.

METHODS

Criteria for considering studies for this review

Types of studies

Studies must be RCTs meeting the selection criteria. Blinding is unfeasible and will not be included. Only studies where the original decision to randomise patients to resection or biopsy were included; studies which randomised patients to receive a particular radiotherapy or chemotherapy regimen and subsequently stratified patients (in a non-random fashion) according to degree of surgery were not accepted. Foreign language journals were eligible for inclusion.

Types of participants

Patients with a presumed HGG from clinical examination and imaging (CT or MRI) will be included. Patients should be stratified for age and performance status to provide comparable treatment arms. The most commonly used measure of performance status is the Karnofsky Performance Score (KPS) (Karnofsky 1948).

Types of interventions

- ***Biopsy:*** This will include all procedures involving sampling of a tumour. It can be done freehand, although currently a stereotactic procedure is preferred. Variations of the procedure include the use of a frame or bony landmarks for calibration, and CT or MRI as the imaging modality, all of which will be appropriate for inclusion.

- ***Resection*** : This includes all procedures where the pre-operative aim is to remove more tumour than is necessary for pathology. Resection is often graded as either attempted total, partial, or palliative de-bulking, all of which will be eligible for inclusion. Assessment of complete resection can be by the surgeons operating opinion, or more reliably by post-operative imaging. A complete resection is 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). It is believed that a more complete resection will lead to a longer survival. There are numerous adjuncts to modern resections, and as none of these are part of standard practice or have a clear evidence base, trials including any of these procedures will be valid to be included in our own study.

Types of outcome measures

Primary outcomes

Median Survival Time (MST): this will be a time with confidence intervals. Also included will be hazard ratios, and percentage of survivors at defined periods.

Secondary outcomes

For each of these the assessor should be blinded (as well as possible) and independent from the trial.

- Time to Progression (TTP): open and thorough criteria should be used to define recurrence, for example the MacDonald criteria (MacDonald 1990) which defines progression according to clinical symptoms, imaging or increasing steroid therapy.
- QOL: a valid and reliable measure should be used, for example the linear analogue scale assessment or the Functional Assessment of Cancer Therapy - Brain.
- Symptom control: improvement of symptoms, or a prolonged maintenance of symptoms without deterioration.
- Morbidity: clinically assessed at regular intervals following the procedure using a pre-specified checklist, ideally.
- Mortality: immediately following procedure and at 30 days.

Follow up should be at sufficient intervals to allow sensitivity in the detection of adverse effects.

Search methods for identification of studies

Electronic searches

The same principle was used to search each database. Firstly the terms and phrases identifying randomized or clinical 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 i.e. biopsy versus resection, was also combined with “OR”. These terms 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 complete search strategies are described in Table 1; only the MEDLINE strategy is described in the review.

Table 1. Complete Search Strategy for Identification of Studies

Database	Search

Table 1. Complete Search Strategy for Identification of Studies (*Continued*)

CANCERLIT (1983 - Feb 2003)	This database was searched using the same strategy as that used for MEDLINE.
EMBASE (1980 to Jan Week 1 2007)	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* 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 "brain-biopsy"/all subheadings 30. explode "brain-surgery"/all subheadings 31. explode "neurosurgery"/all subheadings 32. biops* near resect* 33. extent of resection* 34. explode "multimodality-cancer-therapy"/all subheadings 35. cytoreduct* near surg* 36. #29 or #30 or #31 or #32 or #33 or #34 or #35 37. #28 and #36 38. #17 and #37

Table 1. Complete Search Strategy for Identification of Studies (*Continued*)

BIOSIS PREVIEWS (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
SCIENCE CITATION INDEX (1981 to 2007)	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"

Table 1. Complete Search Strategy for Identification of Studies (*Continued*)

CENTRAL on the Cochrane Library (Internet version)	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 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. BIOPSY 12. NEUROSURGERY 13. NEUROSURGICAL PROCEDURES 14. STEREOTAXIC TECHNIQUES 15. CRANIOTOMY 16. (biopsy and (versus and resection)) 17. (biops* near resect*) 18. (extent near resection) 19. (#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18) 20. (#10 and #19)
Physician Data Query (PDQ): http://www.nci.nih.gov/cancer-topics/pdq	Search form - all types of brain tumours - adults, children Treatment Active and closed Phase III and IV
meta-Register of Controlled Trials (mRCT): http://www.controlled-trials.com/mrct	Keywords: brain, biopsy, glioma

- MEDLINE (1966 to Jan Week 1 2007) Search Strategy.

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 tumo?r*

46. neuroectodermal tumo?r*

47. ependymoma*

48. oligodendroglioma*

49. or/38-48

50. explode "Biopsy"/ all subheadings

51. explode "Neurosurgical-Procedures"/all subheadings

52. explode "Neurosurgery"/all subheadings

53. biops* near resect*

54. extent of resection

55. cytoreduct* near surg*

56. craniotom*

57. or/50-56

58. #47 and #57

59. #37 and #58

Searching other resources

The references of all identified studies were to be searched to identify more trials.

Hand searching

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 following provided e-mail feedback on any current or pending RCTs for the 2007 update:
MJ van den Bent, M Fabbro, K Hopkins, F Laigle, D Netuka, A Obwegeser, G Pesce, M Weller, W Wick, J Wolff.

Data collection and analysis

Identification of studies was made in two stages. Abstracts returned by the original search were examined independently by two researchers and screened to see if they met inclusion or exclusion criteria. Next, full texts of the selected reviews were obtained, which were further examined for inclusion or exclusion. At all times any disagreements were resolved through discussion. If sufficient data was not available for assessment then the relevant authors of the trial were contacted.
Any trials deemed relevant were critically appraised by checklist (Fowkes 1991) and the criteria reported in the NHS CRD Report No. 4. Tables were constructed to summarise internal and external validity (Juni 2001). Furthermore trials were allocated according to risk of bias, referred to in the Cochrane Handbook (Higgins 2005).
Data from included studies were to be extracted and analysed. In the case of missing data, the authors were to be contacted. For continuous data Hazard Ratios (HR) with 95% Confidence Intervals (CI) and a p-value were to be calculated. For dichotomous data Peto Odds Ratios (OR) with 95% CI and a p- value were to be calculated. Normal continuous data were to have been summated using the weighted mean difference.
A funnel graph of trial effect versus trial size was to be constructed with the data from all included studies entered in order to investigate the likelihood of publication bias.

RESULTS

Description of studies

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

Included studies

One RCT of biopsy or resection for HGG was identified (Vuorinen 2003). This was a single institution study of people over the age of 65 years accrued between 1993 and 1996. A full analysis of its design is presented in Characteristics of included studies and Table 2.

Table 2. Design Characteristics

Study	Setting	Age	Inclusion criteria	Exclusion Criteria	Treament Regime	Outcome measures

Table 2. Design Characteristics (*Continued*)

Vuorinen 2003	A single university teaching hospital in Finland.	65 or older	1. Radiologically malignant supratentorial glioma 2. KPS greater than 60 at time of randomisation 3. patient older than 65 at time of randomisation 4. 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 post-intervention management guidelines or protocol.	Survival. Time of deterioration (defined as not able to live at home; time after which patient stayed permanently in hospital or in nursing home). Postoperative complications.

Thirty patients were randomised. Sixteen were allocated biopsy and 14 resection. There were a significant number of patients who had other conditions in both arms. Three patients in the biopsy group had other conditions (two metastasis, one haematoma). Four patients in the resection group were excluded (lymphoma, haematoma, infarct) and one withdrew consent after randomisation.

Excluded studies

Ten other studies were identified but then excluded. Two studies were not RCTs but literature reviews (Kreth 1993; Quigley 1991). Three studies were prospective but assessed symptoms only (Fadul 1988; Sawaya 1998; Whittle 1998). Another study was a RCT, however the patients were not randomised to biopsy or resection but rather to different chemotherapy regimens and were subsequently analysed according to the extent of tumour resection (Wisoff 1998). Four other RCTs have assessed surgery for malignant glioma, but they did not specifically compare biopsy versus resection. Two were on new surgical techniques, namely fluorescence-guided surgery (Stummer 2006) and neuronavigation (Willems 2006), and are described further in the tables for interest. The other two RCTs considered adjuncts to resection, namely the application of chemotherapy wafers to the resection cavity (Valtonen 1997; Westphal 2003), which is the subject of another Cochrane review.

Ongoing Studies

A RCT of biopsy versus resection in the elderly with HGG is due to commence in 2007 in France under ANOCEF.

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

Risk of bias in included studies

There were numerous errors in the methodology of the single included study. Full analyses of the internal and external validity of this study are provided in additional tables (Table 3 and Table 4).

Table 3. Internal Validity

Characteristic	Study
	Vuorinen 2003
Power calculation?	No
Proper randomisation?	Not stated
Groups similar at baseline?	No
Blinding	Investigators: No; Outcome assessors: No; Patients: No.

Table 3. Internal Validity (*Continued*)

Eligibility criteria stated?	Yes
Objective outcome measures?	Only survival, others not
Analysis on ITT basis?	Yes
All patients accounted for?	Not stated
Withdrawals specified?	No
Withdrawal reasons given?	No
Conflict of interest?	No

Table 4. External Validity

Study	Sample Size	Age (median & range)	Sex (%M:F)e	Histology	KPS	Extent of Surgery	Subgroups analysed	Follow up
Vuorinen 2003	6n=30. Resection=14 Biopsy=1.	Resection: 70 (66-80). Biopsy: 72 (67-79)	Data unavailable	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 (60-90). Biopsy: 70 (60-90)	Total - 2; Subtotal - 7; resection - 1.	None	Up to 590 days

- Power: The authors did not provide a sample size calculation based on the primary endpoint of survival. If we assume a median survival of 100 days in the biopsy arm and estimate the number of patients in each arm required to show an increase in survival of 30 days in the resection arm with a power of 80%, an accrual period of two years and follow up period of two years, a trial of 500 patients (250 in each arm) would be required.

- Randomisation: The method of randomisation was not described. It is uncertain where there could have been any allocation bias. No stratification for age or KPS was performed at randomisation.

- Error in the Methods section: states that only patients with a KPS of greater than 60 were included. (four in the biopsy group and two in the resection group had a KPS equal to 60).

- Bias: There are inequalities in the characteristics of the patients in the two arms:

a) 85% of patients in the biopsy arm were 70 years or over compared with 50% in the resection arm.

b) 23% of patients in the biopsy arm had a KPS greater than or equal to 80 compared with 60% in the resection arm.

c) 77% of patients in the biopsy arm received radiation therapy compared with 90% in the resection arm.

- Results: Data on only 13 of 16 patients in the biopsy arm (81%) and 10 out of 14 patients in the resection arm (71%) were provided. Time to Deterioration as defined here will depend on the social support system that each individual patient has.

Effects of interventions

Search Results

The original electronic database searches yielded a total of 2100 citations:

- MEDLINE- 177
- CCTR - 51
- CCN (Specialised Register of Trials) - 300
- CANCERLIT- 133
- EMBASE- 743
- Biosis - 370
- Science Citation Index - 326

In addition, the checking of reference lists, hand searching and personal communications failed to reveal any relevant trials.

Updates

The update in February 2003 revealed an additional 271 references from MEDLINE from 1999-Feb week 12003; 44 additional references from EMBASE and one reference from Cochrane Library. Three studies for potential inclusion were identified, but two were then excluded. The second update in January 2007 identified four RCTs that were considered and then excluded.

Primary outcome measures

Survival was recorded from the time of surgery for the valid study group (but not the total study group). This was demonstrated in a Kaplan Meier plot and compared by non-parametric log rank chi-square test. The difference in survival time was statistically significant (p = 0.0346). Median survival times (MST) were: biopsy group (85 days, 95%CI: 55 to 157), resection group (171 days, 95%CI: 146 to 278). This difference was statistically significant (p = 0.035).

Secondary outcome measures

Time to Deterioration (as defined by "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. This difference was statistically significant (p = 0.0566) but no CI were given. QOL no quality of life data were recorded. No patient in the biopsy group had a procedure-related complication however one of the 10 patients in the resection group had a post-operative haematoma that required re-operation.

DISCUSSION

There is an extensive literature on surgery for malignant glioma, and a comprehensive review of this has recently been published (Proescholdt 2005). Unfortunately most of the studies are of phase II trial design. Selection bias is particularly important to overcome with regard to HGG, as it is known that patients undergoing resection are fitter than those undergoing biopsy, necessitating randomisation and stratification by prognostic factors.

Our literature search only identified one trial that met our entry criteria (Vuorinen 2003). This study, however, contained methodological shortcomings, but was reported as being in favour of resection over biopsy. Due to errors in trial design and under-powering, the findings are tainted by a high likelihood of being affected by bias and chance. The most appropriate conclusions from his trial are that it is of insufficient reliability to be used to influence treatment decisions. It should be viewed as evidence that RCTs are feasible in the area and used as a building block for further RCTs.

When a patient presents with a space occupying lesion, radiology is accurate for the diagnosis of a tumour but it is not accurate for the identification of the type of tumour (Kondzioloka 1993; Murphy 2002). A pathological diagnosis is desirable to allow identification of other treatable conditions such as cerebral abscess, and to allow identification of tumours with specific treatments such as germinomas. 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. Resection undoubtedly does give a more thorough sample of tissue, but whether this would lead to any management alteration over a biopsy diagnosis has not been studied.

One prospective series of patients who were biopsied then resected a mean of 3 weeks later found that biopsy correctly guided therapy in 91% of cases (Woodworth 2005). Biopsy sampling 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 malignant glioma may lead to a delay in treatment. Within clinical trials, this may lead to some patients with low grade glioma being included in the

biopsy arm that 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 a low risk procedure, with a morbidity rate from retrospective series of around 3.5% and a mortality rate of <1% (Hall 1998) and can be carried out as a day procedure. The results of prospective studies of complications following neurosurgery in brain tumours are summarised in Table 5. In two prospective series resection had a morbidity rate of 32% and a mortality of 1.7-3.3% (Fadul 1988; Sawaya 1998). In eloquent areas surgery still carries a low risk of morbidity and can improve dysphasia when intra-operative brain mapping and awake craniotomy is utilised (Whittle 1998). Regarding relief of symptoms from resection, there is some evidence that 32% will improve, while 58-76% were not discernibly different (Fadul 1988; Sawaya 1998). However, while surgery can improve some symptoms, it can also create new ones.

Table 5. Complications following neurosurgery for brain tumours

Study	Numbers	Mortality	Morbidity	Haematoma	Abscess	Seizure
Vuroinen 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%	-	-	-

Only broad guidelines can be made and treatments must be considered on an individual basis. Biopsy may be the only option for certain deep seated tumours (thalamic, callosal, brainstem), while small superficially placed frontal tumours can be resected completely with little difficulty. Due to the associated risks of resection, biopsy is currently preferred for those with poor performance status (KPS < 70), elderly (> 60 years), lesions in an eloquent area and diffuse lesions (multi-lobe or multi-focal). In other selected groups of patients the risks of resection may be lower, and there may be a greater likelihood for benefits from surgery. In some patients the prognosis may be deemed so poor that treatment would only be palliative, and histology would not affect this management direction. Nevertheless, biopsy tends only to be withheld when the patient is moribund.

Histological diagnosis is desirable for the management of a suspected brain tumour, and can be achieved through either 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. Biopsy however 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 man-

agement of patients with malignant glioma can be made.

Until there is concrete evidence one way or the other, it is important to consider each case individually and for the surgeon to carry out the procedure which he deems to be the most appropriate for that particular patient, taking into account the risks and benefits. Such decisions are best made at a multi-disciplinary team meeting (NICE guidance).

Given the lack of 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 RCTs of biopsy versus resection for malignant glioma.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Vuorinen 2003

Methods	RCT
Participants	30 patients were enrolled from a single university hospital between 1993-1996. 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 were not an exclusion. No stratificatio for age or performance status.
Interventions	Stereotactic Biopsy: Open craniotomy and resection. A pre-randomisation brain scan (CT or MRI) was performed. Procedures were performed by an experienced neuro-surgeon. An estimate of extent of resection was made from a postoperative brain scan in those undergoing resection between days one and three. Clinical evaluation was performed one week after surgery and Karnofsky 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 square test.
Notes	4 exclusions from resection group and 3 from biopsy group

RCT = Randomised Controlled Trial

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

Fadul 1988	Prospective study of surgery considering primarily morbidity and mortality only.
Kreth 1993	Literature review not a RCT.
Quigley 1991	Literature review not a RCT.
Sawaya 1998	Prospective study of surgery considering primarily morbidity and mortality only.
Stummer 2006	RCT considering fluorescent guided surgery compared to normal resection. 322 patients aged between 23-73 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. Some questions remain about the methods used in the trial. In brief, there was a high exclusion rate, and some concern over why some in the treatment arm dropped out before radioterhapy. Definitions of the two main outcome measures of complete resection and recurrence are also not robust or stringent enough for clinical use. In addition the patients were very highly selected and don't reflect those in practice. Finally, there is some concern that the more aggressive resections in the treatment arms resulted in greater post-operative morbidity. Although this trial has been cited as evidence for the benefit of more aggressive resection, the questions raised above

(*Continued*)

	demand that a cautious approach is required.
Valtonen 1997	RCT of chemotherapy wafers to cavity after resection compared with normal resection. Discussed further in the Cochrane Review 'Chemotherapeutic wafers for HGG.'
Westphal 2003	RCT of chemotherapy wafers to cavity after resection compared with normal resection. Discussed further in the Cochrane Review 'Chemotherapeutic wafers for HGG.'
Whittle 1998	Prospective series of awake craniotomy and cortical mapping in patients with dysphasia.
Willems 2006	RCT of neuronavigation for resection compared with normal resection. 45 patients were accrued in total, 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. It was felt by the surgeon that neuronavigation was useful, and it didn't lead to considerably longer operating times or greater adverse events. There is a suggestion that there were fewer acute defecits in the first few days post-operatively in the neuronavigation arm, and that the treatment arm had a lower use of steroids. The main flaws with this study are that it's patients were highly selected, and possibly that the non-treatment arm had a slighltly better prognosis at baseline. This fact and the conincidental early deaths of 3 patients in the treatment arm, together with the low power to detect effects, put the trial at a significant risk of a type 1 error.
Wisoff 1998	Patients were not randomized to type of surgery but to different chemotherapy regimens. They were then stratified according to extent of tumour resection, and the results analysed.

DATA AND ANALYSES

This review has no analyses.

WHAT'S NEW

Last assessed as up-to-date: 4 January 2007.

19 August 2008	Amended	Converted to new review format. The introduction, description of studies, methodology and discussion have been modified with each subsequent update.

HISTORY

Protocol first published: Issue 1, 2000

Review first published: Issue 1, 2000

15 April 2007	Amended	Minor update: 15/04/07. New studies sought but none found: 05/01/07. New studies found and included or excluded: 04/02/03. Conclusions changed: 15/04/07 Reformatted: 15/04/07.
23 February 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Sarah Metcalfe was the initial reviewer in 1999. Robert Grant aided in the search strategy and edited the review prior to the first submission. He updated the review in 2000 and substantially updated the review in 2003. Michael Hart updated the review in 2007.

DECLARATIONS OF INTEREST

None known.

NOTES

February 2003 - review updated, one new RCT identified. Did not affect conclusions of review.

January 2007 - review updated, no new trials identified.

INDEX TERMS

Medical Subject Headings (MeSH)

Biopsy [*methods]; Brain Neoplasms [pathology; *surgery]; Craniotomy; Glioma [pathology; *surgery]; Randomized Controlled Trials as Topic; Risk; Stereotaxic Techniques

MeSH check words

Humans