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[Intervention Review]

Image guided surgery for the resection of brain tumours

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ABSTRACT

Background

Extent of resection is believed to be a key prognostic factor in neuro-oncology. Image guided surgery uses a variety of tools or technologies to help achieve this goal. It is not clear whether any of these, sometimes very expensive, tools (or their combination) should be recommended as part of standard care for patient with brain tumours. We set out to determine if image guided surgery offers any advantage in terms of extent of resection over surgery without any image guidance and if any one tool or technology was more effective.

Objectives

To compare image guided surgery with surgery either not using any image guidance or to compare surgery using two different forms of image guidance. The primary outcome criteria was extent of resection and adverse events. Other outcome criteria were overall survival; progression free survival; and quality of life (QoL).

Search methods

The following databases were searched, the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 1, 2013), MEDLINE (1948 to March, week 10, 2013) and EMBASE (1970 to 2013, week 10). Reference lists of all identified studies were searched. Two journals, the Journal of Neuro-Oncology and Neuro-oncology, were handsearched from 1991 to 2013, including all conference abstracts. Neuro-oncologists, trial authors and manufacturers were contacted regarding ongoing and unpublished trials.

Selection criteria

Study participants included patients of all ages with a presumed new or recurrent brain tumour (any location or histology) from clinical examination and imaging (computed tomography (CT), magnetic resonance imaging (MRI) or both). Image guidance interventions included intra-operative MRI (iMRI); fluorescence guided surgery; neuronavigation including diffusion tensor imaging (DTI); and ultrasonography. Included studies had to be randomised controlled trials (RCTs) with comparisons made either with patients having surgery without the image guidance tool in question or with another type of image guidance tool. Subgroups were to include high grade glioma; low grade glioma; brain metastasis; skull base meningiomas; and sellar or parasellar tumours.

Data collection and analysis

Two review authors independently assessed the search results for relevance, undertook critical appraisal according to known guidelines, and extracted data using a pre-specified pro forma.

Main results

Four RCTs were identified, each using a different image guided technique: 1. iMRI (58 patients), 2. 5-aminolevulinic acid (5-ALA) fluorescence guided surgery (322 patients), 3. neuronavigation (45 patients) and 4. DTI-neuronavigation (238 patients). Meta-analysis was not appropriate due to differences in the tumours included (eloquent versus non-eloquent locations) and variations in the image guidance tools used in the control arms (usually selective utilisation of neuronavigation). There were significant concerns regarding risk of bias in all the included studies, especially for the study using DTI-neuronavigation. All studies included patients with high grade glioma, with one study also including patients with low grade glioma. The extent of resection was increased with iMRI (risk ratio (RR) (incomplete resection) 0.13, 95% CI 0.02 to 0.96, low quality evidence), 5-ALA (RR 0.55, 95% CI 0.42 to 0.71) and DTI-neuronavigation (RR 0.35, 95% CI 0.20 to 0.63, very low quality evidence). Insufficient data were available to evaluate the effects of neuronavigation on extent of resection. Reporting of adverse events was incomplete, with a suggestion of significant reporting bias. Overall, reported events were low in most studies, but there was concern that surgical resection using 5-ALA may lead to more frequent early neurological deficits. There was no clear evidence of improvement in overall survival (OS) with 5-ALA (hazard ratio (HR) 0.82, 95% CI 0.62 to 1.07) or DTI-neuronavigation (HR 0.57, 95% CI 0.32 to 1.00) in patients with high grade glioma. Progression-free survival (PFS) data were not available in the appropriate format for analysis.

Data for quality of life (QoL) were only available for one study and suffered from significant attrition bias.

Authors' conclusions

There is low to very low quality evidence (according to GRADE criteria) that image guided surgery using iMRI, 5-ALA or DTI-neuronavigation increases the proportion of patients with high grade glioma that have a complete tumour resection on post-operative MRI. There is a theoretical concern that maximising the extent of resection may lead to more frequent adverse events but this was poorly reported in the included studies. Effects of image guided surgery on survival and QoL are unclear. Further research, including studies of ultrasound guided surgery, is needed.

PLAIN LANGUAGE SUMMARY

Imaging guided surgery for brain tumours

Background

Surgery has a key role in the management of many types of brain tumour. In some types of brain tumour the amount that can be removed by the surgeon is very important in helping patients live longer and feel better. However, sometimes removing a brain tumour can be difficult, because it either looks like normal brain tissue or is near brain tissue that is very important to making people function normally. New methods of visualising tumours during surgery have been developed to help surgeons better identify tumour from normal brain tissue.

Question

1. Is image guided surgery more effective at removing brain tumours than surgery without image guidance?

2. Is one image guidance technology or tool better than another?

Study characteristics

Our search strategy was up to date as of March 2013. We found four trials looking at four different types of tools to help improve the amount of tumour that is removed. The tumour that they looked at was usually high grade glioma but one study also included patients with low grade glioma. Imaging interventions used during surgery included magnetic resonance imaging (iMRI) during surgery to assess the amount of remaining tumour, or a fluorescent dye (5-aminolevulinic acid (5-ALA)) to mark out the tumour. Two trials used pre-operative imaging to map out the location of a tumour, which was then used at the time of surgery to guide the resection (neuronavigation). All the studies were at significant risk of bias and some were small and stopped early. Others were funded by the manufacturers of the image guidance tool involved.

Key results

We found low quality evidence that using image guided surgery can lead to more of the tumour being removed surgically in some people. It has not been proven that any of the techniques that were evaluated improve overall survival. Data about how each technique

can affect a patient's quality of life was poorly reported. The side effects of each technique were also poorly reported, but they did not appear to be more common with image guided surgery. There is a concern that taking out more of the tumour using 5-ALA can lead to patients having a type of stroke early after surgery but long-term the risk seems to be no different between techniques. There was very low quality evidence for neuronavigation and no trials were identified for ultrasound guidance.

Quality of the evidence

Evidence for image guided surgery in removing brain tumours is sparse and of low quality. Further research is needed to assess two main questions.

1. Is removing more of the tumour better for the patient in the long-term?

2. What are the risks of making a patient symptomatically worse by taking out more of the tumour, and how may this affect a patient's quality of life?

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Image guided surgery compared to standard surgery for high grade glioma

Patient or population: high grade glioma
Settings: specialist centres
Intervention: image guided surgery
Comparison: standard surgery

Outcomes	Illustrative comparative rate* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed rate	Corresponding rate				
	control	image guided surgery				
Complete resection - iMRI	**40 per 100**	**92 per 100** (42 to 99)	**RR 0.13** (0.02 to 0.96)	49 participants (1 study)	⊕⊕◯◯ **low**	Small study of highly selected participants with potential bias in allocation and performance
Complete resection - 5-ALA	**40 per 100**	**67 per 100** (57 to 75)	**RR 0.55** (0.42 to 0.71)	270 participants (1 study)	⊕⊕◯◯ **low**	Highly selected participants with potential bias in allocation and performance
Complete resection - DTI-neuronavigation	**40 per 100**	**79 per 100** (62 to 88)	**RR 0.35** (0.20 to 0.63)	85 participants (1 study)	⊕◯◯◯ **very low**	Small study of highly selected participants at very high risk of allocation bias (see discussion)

*The basis for the **assumed risk** is the weighted mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

BACKGROUND

Description of the condition

Tumours of the central nervous system (CNS) are an eclectic ensemble characterised by a vast histological and anatomical variety. The World Health Organization (WHO) Classification divides tumours of the CNS into seven categories, tumours of the neuroepithelial tissue; tumours of the cranial and paraspinal nerves; tumours of the meninges; tumours of the haematopoietic system; germ cell tumours; tumours of the sellar region; and metastatic tumours (Loius 2007). Primary brain tumours (those that start and usually remain in the CNS) commonly arise from the supporting glial cell architecture, and of these glioblastoma is the most frequent and malignant histological subtype (Ohgaki 2009). Secondary brain tumours or metastasis (which spread to the CNS from a tumour elsewhere in the body) are the most common overall, accounting for almost half of all CNS tumours.

Brain tumours usually present with headaches, neurological deficits or seizures, either alone or in combination. Treatment choices usually include a combination of surgery (either biopsy or resection), radiotherapy and chemotherapy. National guidelines recommend that the management of a patient with a CNS tumour should be discussed in a multi-disciplinary team (MDT) and individually tailored to patients' needs (NICE 2006).

Description of the intervention

Intra-operative magnetic resonance imaging (iMRI)

This intervention involves the same principles as a routine MRI but is performed in the operating theatre. Intra-operative MRI (iMRI) involves either a specific portable MRI scanner or a parallel stationary MRI scanner in an adjacent diagnostic room. Acquisition of the iMRI is aimed at providing a real-time assessment of the tumour resection, allowing the possibility of a further resection in the same operative session (Black 1997; Seifert 2003). Uptake of this method has been limited by low field strengths (at least initially, although now higher field strength systems are becoming available), additional operating time, equipment size and associated costs.

Neuronavigation

This refers to the computational process involved in representing a real spatial position (in 'world space') onto previously acquired and displayed imaging data ('image space'). Pre-operative imaging can be used to localise a lesion, perform tailored craniotomies, and estimate the extent of resection (although this final point can only be confirmed after further imaging). A major limitation of this technique is the phenomenon of intra-operative brain shift, where the pre-operative anatomy alters during the approach and tumour resection thereby reducing accuracy. Advantages include the potential to use functional brain imaging studies to define eloquent or invaded tissues (such as diffusion tensor imaging to define the white matter tracts). Although this system usually uses images acquired pre-operatively, it has still been included as the use of the imaging is intra-operative, and subsequent repeat imaging intra-operatively (for example computed tomography (CT) or MRI) can be used for guidance too, e.g. iMRI.

Ultrasonography

Ultrasonography (US), in either two or three dimensions, visualises structures by recording the reflections of echoes of pulses of ultrasonic waves (frequency greater than 20 megahertz (MHz)) directed into the tissue of interest. Freehand movement of a US probe allows acquisition of image volume in three dimensions (3D). Updated 3D US volumes can be created at any time during surgery. Advantages include easy repeatability. The main disadvantage is operator variability, whereby efficacy depends on skill and experience (Unsgaard 2006).

Fluorescence guided surgery

This most commonly uses 5-aminolevulinic acid (5-ALA, or Gliolan®) as a natural biochemical precursor of haemoglobin that elicits the synthesis and accumulation of fluorescent porphyrins preferentially in mitotically active tissue such as tumours (Regula 1995). Porphyrin fluorescence can be visualised with a modified microscope using filtered light with the aim of identifying neoplastic tissue (Stummer 1998; Stummer 2000). Limitations include variable intensity of fluorescence depending on tumour characteristics and photobleaching whereby the effect diminishes with time.

How the intervention might work

The extent of surgical resection is believed to be a key prognostic factor in neuro-oncology. For some tumours this is clearly established while for others, particularly high grade glioma, the benefit is less clear (Hart 2011). Although there is a lack of high quality evidence, estimated benefits of gross total resection are that it may extend survival from around 11 to 14 months in glioblastoma and from around 60 to 90 months in low grade glioma (Sanai 2009). Limitations to the extent of surgical resection include the ability to reliably identify residual tumour in theatre and the proximity of the tumour to eloquent tissue. Multiple technologies have been developed to aid intra-operative diagnosis of residual tumour with the aim of extending resection; this information can be used by the surgeon to increase the extent of resection and, therefore, potentially improve prognosis.

Why it is important to do this review

Experience with each different technology is often limited in individual units. Technologies are often seen as an evolution of established techniques and are not subject to the rigorous scrutiny of other new therapies, therefore the level of evidence is often limited to small single institution case series. Direct comparisons between different intra-operative imaging technologies are necessary to limit over-expenditure on redundant products.

Increasing the extent of resection comes with the risk of encroaching upon eloquent brain areas. Potential benefits of more extensive tumour resection need to be balanced with the risk of producing new neurological deficits and reducing quality of life (QoL). This demands an objective assessment of the risks and benefits of each technology.

This review aims to be a comprehensive resource describing the level of evidence and effectiveness for each technology utilising imaging intra-operatively in order to safely maximise resection of brain tumours. A single review was planned due to the potentially small number of eligible studies and to allow a comparison between different image guidance tools. It was also felt that a single study may lend itself better to potential network meta-analyses or economic reviews in the future.

OBJECTIVES

To compare the extent of resection and adverse events of surgery utilising intra-operative imaging tools with:

1. surgery not using any image guidance (to determine if an intra-operative imaging tool is effective), or

2. surgery using a different form of image guidance (to determine if one tool is more effective than another).

METHODS

Criteria for considering studies for this review

Types of studies

Studies had to be randomised controlled trials (RCTs) meeting the selection criteria (described in detail below). We only included studies where the original decision was to randomise patients to a specific intra-operative imaging modality. Studies which randomised patients to receive another treatment regimen (e.g. radiotherapy or chemotherapy) and subsequently stratified patients (in a non-random fashion) according to intra-operative imaging modality were not accepted. Foreign language journals were eligible for inclusion.

Types of participants

Patients with a presumed new or recurrent CNS tumour (any location or histology) from clinical examination and imaging (CT but ideally contrast enhanced MRI) were included. Additional imaging modalities (e.g. positron emission tomography or magnetic resonance spectroscopy) were not mandatory. No age restrictions were applied.

Types of interventions

1. **Intra-operative MRI (iMRI)**: defined as involving either a portable or fixed scanner (and moving either scanner or patient respectively) to acquire image data while the patient remains under anaesthesia, and may be integrated with neuronavigation (see below).

2. **Neuronavigation or image guidance**: defined as system that integrates pre- or intra-operative image data and creates a translation map between 'world space' and 'image space' to allow co-registration of imaging and patient anatomy allowing neuronavigation. Currently, the main trade systems are Brainlab ® (Codman) and Stealth® (Medtronic).

3. **Intra-operative ultrasound (US) in either two (2D) or three dimensions (3D)**: defined as a system that uses freehand movement of an US probe over the region of interest and subsequently generates a volumetric reconstruction allowing neuronavigation intra-operatively. Currently, the main brand of intra-operative 3D US is Sonowand^{TM}.

4. **Fluorescence-guided surgery**: defined as administration of a contrast agent and visualisation intra-operatively with the use of filtered light (usually a specific mode of an operating microscope set to a wavelength of 400 nm). Currently, the main agent used is 5-aminolevulinic acid (5-ALA) marketed under the trade name of Gliolan® by medac.

Types of outcome measures

Primary outcomes

- **Extent of resection**: as defined in follow-up imaging.

Complete resection of all enhancing tissue on MRI scanning within 72 hours of surgery was taken as the primary outcome for high grade glioma. Modern guidelines have given explicit criteria for defining measurable and non-measurable disease with the specific scanning requirements also stated (RANO 2010). Volumetric assessment is potentially a better method of assessment in terms of accuracy and objectivity but is performed less frequently. Intra-operative evaluation of extent of resection by the operating surgeon is a biased and unverifiable method and, therefore, not acceptable (Hensen 2008). Tumour types other than high grade glioma were assessed on delayed MRI by the radiology consultant report.

- **Adverse events**: type (as defined using Medical Dictionary for Regulatory Authorities (MedDRA) criteria) and timing (MedDRA 2008). Examples include: haematoma, wound complications, infection (and site), cerebral spinal fluid (CSF) leak, oedema, seizures and general medical complications. Further procedures required for complications should be noted. Both the total number of complications and complications per patient should be stated.

Secondary outcomes

- **Survival**: is the length of time (in days, weeks or months) from randomisation to death (from any cause).
- **Progression-free survival (PFS)**: open and thorough criteria had to be used to define recurrence according to clinical symptoms, imaging and increasing steroid therapy (Wen 2010).
- **Quality of life (QoL)**: an established grading measure had to be used, for example the EORTC QLQC30/BN-20 and FACT-BrS (Mauer 2008).

Search methods for identification of studies

Electronic searches

We searched the following databases:

- CENTRAL (Issue 1, 2013);
- MEDLINE (from 1946 to March, week 2, 2013)
- EMBASE (from 1974 to week 10, 2013)

The search strategies are presented in Appendix 2.

Searching other resources

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

Handsearching

We undertook a handsearch of both the *Journal of Neuro-Oncology and Neuro-oncology* from 1999 to 2013 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

We contacted the following neuro-oncology experts for information on any current or pending RCTs:
Dr Mitchel S Berger; Professor Hugues Duffau; Dr Roy A Patchell; Dr Chirag G Patil; Dr Christian Senft; Professor Dr Walter Stummer; Professor Dr Manfred Westphal; Professor Dr medicine Wolfgang Wick; Dr Peter WA Willems; Professor Jinsong Wu.

Data collection and analysis

Selection of studies

Identification of studies was made in two stages. Two review authors (MGH and DGB) independently examined and screened abstracts returned by the original search to see if they met inclusion or exclusion criteria. Next, we obtained full texts of the selected reviews, which were further examined and compared with the inclusion and exclusion criteria. At all times any disagreements were resolved through discussion. If sufficient data were not available for assessment then we contacted the relevant authors of the trials.

Data extraction and management

For included studies, two review authors (DGB and MGH) independently abstracted data using a pre-specified form (Table 1) designed to complete the information required for the table of the characteristics of included studies and validity tables (Juni 2001). Differences were reconciled by discussion. Specific data extracted included the following.

- **Patients' characteristics**: age (mean and range), gender, performance status using either the Karnofsky performance score (KPS) (Table 2) (Karnofsky 1948) or World Health Organization (WHO) score (Table 3) (WHO 1982), tumour location, contrast enhancement, and tumour histology.

- **Trial characteristics**: inclusion and exclusion criteria, randomisation methods and stratification, allocation concealment (if applicable), blinding (of whom and when), and statistics. Definitions include extent of resection, progression, and adverse events.

- **Intervention.** iMRI: field strength, timing, type of scanner (separate suite or 'double-donut'), sequences performed, contrast administration, and reporting methods. Neuronavigation: imaging sequences and timing, brand of equipment. 5-ALA: dose and timing, timing of ultraviolet light intra-operatively, microscope used. 3D ultrasound: brand, timing, operator experience. Additionally, the surgical decision making influenced by the intra-operative imaging should be stated.

- **Outcome assessment**: extent of resection (and measurement methods), overall survival, PFS, QoL, and adverse events. Additional quality control information was recorded on follow-up, presence of an intention-to-treat (ITT) cohort, and deviations from the protocol. Additional information was recorded on post-recurrence management.

Assessment of risk of bias in included studies

Trials deemed relevant were critically appraised according to a checklist (Fowkes 1991) and the criteria reported in the NHS CRD Report No. 4 (CRD 2008). We allocated trials according to

risk of bias as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). Specific core risk of bias items that were covered included: selection, performance, detection, attrition, reporting and other. Operator blinding was not always possible; patient and outcome assessment blinding were desirable but not mandatory. Critical appraisal was done by two review authors, independently (MGH and DGB). Any disputes were resolved through discussion. See Table 4 and Table 5 for details of the internal and external validity items.

Measures of treatment effect

- Time-to-event data (survival and PFS): the hazard ratio (HR) and 95% confidence interval (CI) and its inverse variance were abstracted, or calculated using standard methods if not available (Parmar 1998). We stated the overall numbers experiencing the event of interest in the trial period.
- Continuous outcomes (QoL and extent of resection): we abstracted the final value and standard deviation (SD) of the outcome of interest in each treatment arm at the end of the follow-up.
- Dichotomous outcomes (adverse events, mortality, and extent of resection): we abstracted the number of patients in each treatment arm who experienced the outcome of interest in order to estimate a risk ratio (RR).
- Dichotomous and continuous data: we abstracted the number of patients assessed at each endpoint.

Where possible, all data abstracted were those relevant to an intention-to-treat (ITT) analysis. In the case of missing data that was required for the review outcomes, we contacted the study authors. Both review authors (MGH and DGB) performed data extraction and integration to RevMan.

Unit of analysis issues

Extent of resection: complete resection was defined according to the Response Assessment in Neuro-Oncology (RANO) criteria or converted into these units if not presented in this manner (RANO 2010).

Dealing with missing data

In the case of missing data required for the review outcomes, we contacted the study authors. We did not impute missing outcome data.

Assessment of heterogeneity

We assessed heterogeneity between studies by:

1. visual inspection of forest plots;
2. estimation of the percentage heterogeneity (I^2 statistic) between trials which could not be ascribed to sampling variation (Higgins 2009);
3. formal statistical testing of the significance of the heterogeneity (Chi^2 test) (Deeks 2001).

Assessment of reporting biases

We intended to construct a funnel plot of treatment effect versus precision in order to investigate the likelihood of publication bias, if 10 or more studies were identified. If these plots had suggested that treatment effects may not be sampled from a symmetric distribution, as assumed by the random-effects model, we had planned to perform further meta-analyses using the fixed-effect model.

Data synthesis

The identified trials were not deemed suitable for data synthesis and meta-analysis was not performed (see 'Effects of interventions' for a more detailed discussion). However, we specified that the following methods would have been used if appropriate, and they will be used if in the future it is possible to perform data synthesis. Integration of data into RevMan 5 will be performed by the review authors (DGB and MGH). We will pool data if trial characteristics (methodology, patients, interventions, controls and outcomes) were similar.

- Time-to-event data: we will pool HR and variance using the generic inverse variance function of RevMan 5.2.
- Continuous outcomes: we will pool mean differences (MD) between the treatment arms at the end of the follow-up using the MD method if all trials have measured the outcome on the same scale, or using the standardised mean difference (SMD) method if otherwise.
- Dichotomous outcomes: we will calculate the RR for each study and then all studies will be pooled.

We will use random-effects models for all meta-analyses (DerSimonian 1986) but plan to perform further fixed-effect analyses if we find symmetrical distribution.

Subgroup analysis and investigation of heterogeneity

Analyses would have been subgrouped by the type of image guidance tool evaluated. We had also planned to perform subgroup analyses stratified for tumour histology. For example, in patients with high grade glioma, the questions would have been:

1. image guidance tool versus no image guidance tool;
2. image guidance tool A versus image guidance tool B.

Other subgroups would have been:

- low grade glioma (LGG);
- cerebral metastasis;
- skull base meningioma (anterior cranial fossa, sphenoid wing, cavernous sinus, petro-clival and foramen magnum);
- tumours of the sella and parasellar region.

Additional subgroup analyses would be based on whether surgery was for newly diagnosed or recurrent disease.

Sensitivity analysis

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

RESULTS

Description of studies

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

Results of the search

The literature searches revealed 2716 studies from the following sources:

- CENTRAL, 237 references;
- MEDLINE, 646 references;
- EMBASE, 1833 references.

From these, a total of 108 studies were selected for review of the abstracts based on their titles. Of these abstracts a total of 16 articles were chosen for full review (Figure 1).

Figure 1. Study flow diagram.

Included studies

The four included studies (reported in nine articles) are described in detail in Characteristics of included studies.

In summary, we identified one study (reported in three articles) for intra-operative MRI (Senft 2011), one study (reported in four articles) for fluorescence guided surgery (Stummer 2006), and two studies for neuronavigation (Willems 2006; Wu 2007). We did not find any eligible studies of ultrasound (US) guided surgery. All studies included patients with high grade glioma, with one study also including patients with low grade glioma.

The study on iMRI (Senft 2011) recruited 58 patients from a single German neurosurgical unit between 2007 and 2010. Patients had to have a known or suspected glioma that was contrast enhancing and amenable to complete resection. The study compared iMRI with surgery with or without neuronavigation but not fluorescence or US guided surgery.

The study on fluorescence guided surgery (Stummer 2006) recruited 322 patients from multiple centres in Germany between 1999 and 2004. Patients had to have a malignant glioma on imaging. The study compared 5-ALA versus conventional surgery (which could include neuronavigation for planning the approach or localising the tumour only).

The first study on standard neuronavigation (Willems 2006) recruited 45 patients from a single Dutch centre between 1999 and 2002. Patients had to have a single space-occupying lesion. The study compared neuronavigation versus surgery without neuronavigation.

The second study on DTI guided neuronavigation (Wu 2007) recruited 238 patients from a single Chinese unit between 2001 and 2005. Patients had to have a single, unilateral glioma involving the pyramidal tracts. Patients underwent DTI guided surgery versus neuronavigation without DTI. Subgroup analyses included those with high grade and low grade gliomas.

Excluded studies

We excluded seven studies (Characteristics of excluded studies):

- four were not RCTs;
- one trial used repetitive photodynamic therapy (PDT), which essentially precluded analysis of this trial as a test of intra-operative imaging alone;
- one assessed the specificity and sensitivity of intra-operative 3D ultrasound as a diagnostic test rather than a treatment option;
- one did not apply a prospective random allocation process between treatment arms.

Risk of bias in included studies

Full analyses of the internal and external validity of the studies are provided in the 'Additional tables' (Table 4 and Table 5). Summary data for risk of bias are presented in table format (Figure 2; Figure 3). A detailed description is provided below and in the Characteristics of included studies.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

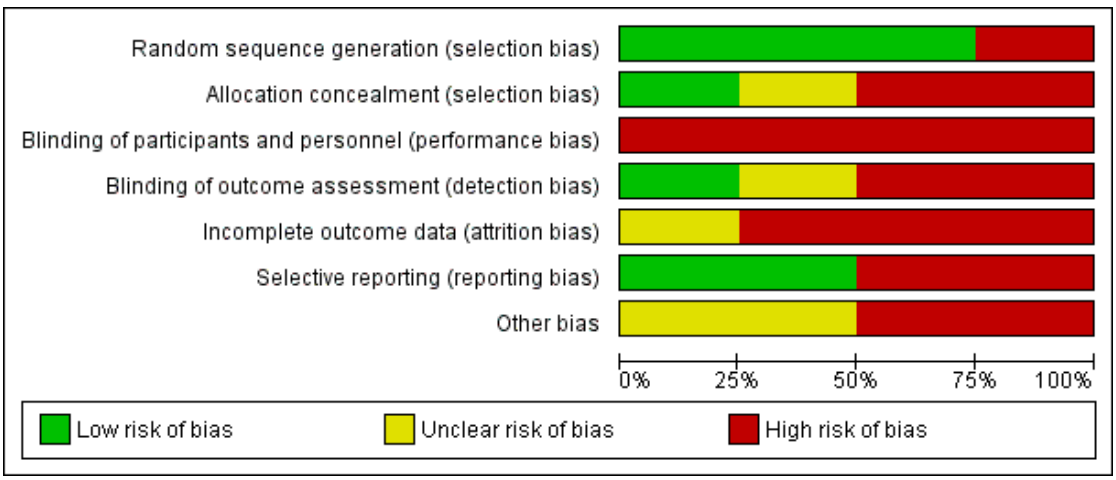
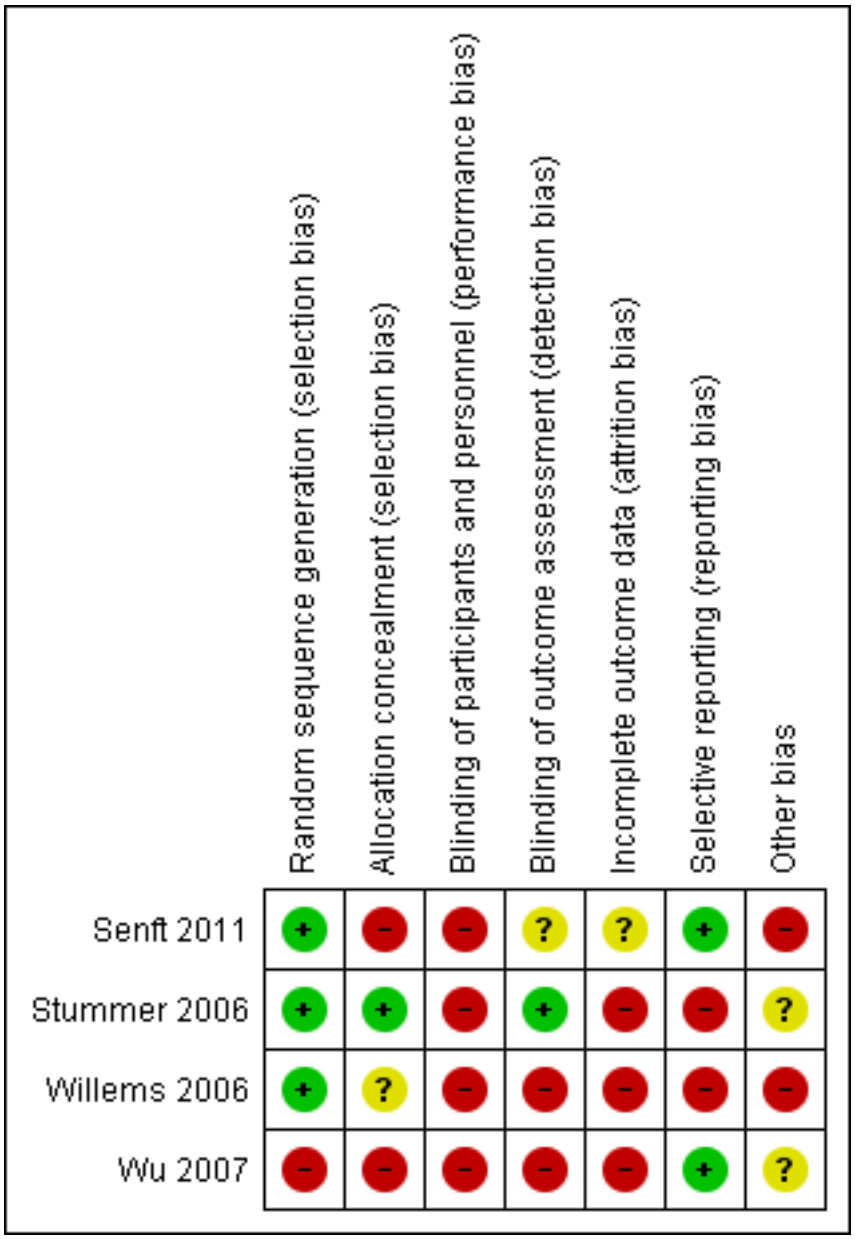


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Randomisation methods were described and were satisfactory in three studies (Senft 2011; Stummer 2006; Willems 2006) and not stated in one (Wu 2007). Allocation concealment was with sealed envelopes and therefore potentially able to be determined prior to allocation in one study (Senft 2011), satisfactory in anothe (Stummer 2006), and not stated in the other two studies. Patients were significantly uneven in the selected baseline variables in one study (Willems 2006) with a greater proportion of eloquent lesions in the standard surgery group and more metastases in the neuronavigation group. This may reflect some degree of selection bias with regard to either randomisation methods or allocation concealment but it may also be due to the low numbers of patients involved.

Subsequent e-mail correspondence with the lead author of one of the papers (Wu 2007) revealed that 'randomisation methods were not strict, and that investigators were aware of allocation prior to enrolment'. Inevitably this would lead to a degree of selection bias.

Blinding

No study was fully blinded to all involved in the study and therefore there was a high risk of performance and detection bias. Two studies used blinded assessment for radiology (Senft 2011; Wu 2007) while another used blinded assessments for both radiological and histological assessment (Stummer 2006).

Incomplete outcome data

A degree of attrition was present in each study and incomplete outcome data may have been a source of bias. For iMRI (Senft 2011), incomplete data were due to alternative pathological diagnoses and no patients were lost to follow-up, therefore the influence of attrition bias was probably low. The data for 5-ALA (Stummer 2006) included 270/322 in the full analysis and 251 in the per protocol analysis but withdrawals were fully specified. For neuronavigation (Willems 2006), the analysis for extent of resection included a subgroup of the total patient population (34/45 patients for tumour volume and 40/45 for contrast enhancing volume) and QoL at three months only included 64.5% of all eligible patients. For neuronavigation-DTI (Wu 2007), data for the outcomes of interest were incomplete for extent of resection, survival and adverse events, albeit in a small proportion of patients. Furthermore, a proportion of patients were excluded due to 'non-glial' histology.

Selective reporting

A single study reported all outcomes and was therefore at low risk of reporting bias (Senft 2011). One study selectively reported data for low grade gliomas (Wu 2007). There was some concern that full outcome data were not presented in the form of figures and appropriate statistics for survival, PFS and adverse events for 5-ALA, which may put the trial at risk of reporting bias (Stummer 2006). A study of neuronavigation did not present full data for survival, QoL or adverse events (Willems 2006). Adverse event data in all studies were particularly poorly reported in terms of total number of events, number of patients with multiple events, and timing of events.

Other potential sources of bias

The standard neuronagivation study (Willems 2006) was stopped early but no reason was given. We attempted to contact the authors of the trial to obtain more details but unfortunately we did not receive a response. The iMRI study (Senft 2011) was stopped early after an interim analysis. One of the authors for the iMRI study received an honorarium from Medtronic (who manufactured the iMRI machine used in the study), although it was emphasised that no funding was involved in the study. The study of 5-ALA (Stummer 2006) was sponsored by medac GmbH (who manufacture Gliolan®) and they were involved in the study design, quality assurance and quality control but had no role in the interpretation of the data and the corresponding author had final responsibility for the article (although the author was a paid consultant to both medac GmbH and Zeiss who manufacture the microscopes used for 5-ALA). Conflicts of interest were not stated in two studies (Willems 2006; Wu 2007).

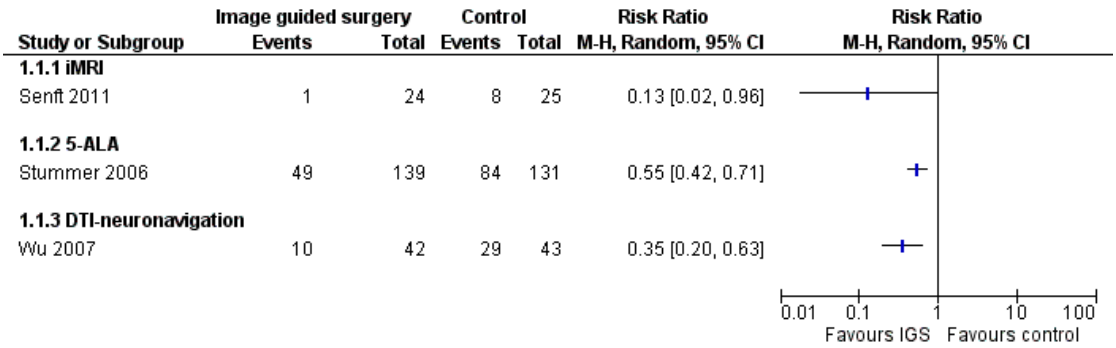
Effects of interventions

See: **Summary of findings for the main comparison** Image guided surgery compared to standard surgery for high grade glioma

Extent of resection

Meta-analysis was not appropriate due to differences in the tumours included (eloquent versus non-eloquent locations) and variations in the image guidance tools used in the control arms (usually selected utilisation of neuronavigation) (see Analysis 1.1). Due to the small number of studies (four) a funnel plot was not performed. The risk ratio (RR) for the extent of resection in patients with high grade glioma favoured the experimental arms in the three studies reporting this outcome, indicating a lower risk of having an incomplete resection with the intervention (Figure 4).

Figure 4. Forest plot of comparison: 1 Image guided surgery versus control, outcome: 1.1 Incomplete resection (high grade glioma).



- **iMRI**: complete tumour resections were achieved in 23/24 (96%) of participants in the intervention arm group compared with 17/25 (68%) of participants in the control arm (RR for incomplete resection 0.13, 95% confidence interval (CI) 0.02 to 0.96, low quality evidence).
- **5-ALA**: complete resection was performed in 90/139 (65%) of the intervention arm versus 47/131 (36%) of the control arm (RR for incomplete resection 0.55, 95% CI 0.42 to 0.71, low quality evidence).
- **Neuronavigation**: complete resection was achieved in three participants in the control group and in five in the neuronavigation group. However, there was significant attrition, with not all patients having complete imaging, and the denominators for these figures were not stated precluding meta-analysis.
- **Neuronavigation with DTI**: among the 85 participants with high grade glioma (HGG), complete tumour resections were achieved in 32/42 in the DTI arm versus 14/43 in the control arm (RR for incomplete resection 0.35, 95% CI 0.20 to 0.63, very low quality evidence). Among the 129 participants with low grade glioma (LGG), complete tumour resections were achieved in 40/61 in the DTI arm versus 42/68 in the control arm (no significant difference).

We considered this evidence to be of low to very low quality (Summary of findings for the main comparison).

Adverse events (AEs)

AEs were reported in an inconsistent manner between trials and not according to the pre-specified manner required in our protocol. Specifically, data were not available for: patients at risk; patients with multiple events; timing of events; outcomes of events. Therefore, we adopted a descriptive method using the data available to describe the AEs in each trial.

- **iMRI**: participants with new or aggravated neurological deficits were present in 2/25 (8%) of participants in the conventional group and 3/24 (13%) participants in the intra-operative MRI group; intra-operative imaging had not led to continuation of tumour resection in any of the participants. Two participants had symptomatic haematomas, which were not attributable to the use of intra-operative MRI. In one patient, haemianopia was deliberately accepted due to tumour extension around the temporal horn of the lateral ventricle involving the optic radiation. No wound infections were reported. Due to the low number of events, RRs and CIs were not deemed appropriate.
- **5-ALA**: AEs were present in 58.7% of the intervention arm versus 57.8% of the control arm. Neurological AEs were present in 42.8% of the intervention arm (7.0% grade 3 to 4) and 44.5% of the control arm (5.2% grade 3 to 4). Significant neurological AEs were 12.4% in the intervention arm versus 11.6% in the control arm. The number of participants with a deterioration in the National Institute of Health Stroke Score (NIH Stoke Scale) compared to baseline tended to be higher in the intervention arm at 48 hours (26.2% with 5-ALA versus 14.5% in the control arm) but not at 7 days (20.5% versus 10.7%), 6 weeks (17.1% versus 11.3%) and 3 months (19.6% versus 18/6%). No denominators were given for each result, preventing the calculation of the RR and CI.
- **Neuronavigation**: new or worsened neurological deficits were present at three months in 45.5% of participants in the control group and 18.2% in the neuronavigation group. During the first three months after surgery, seven participants (31.8%) in the control group and seven (30.4%) in the neuronavigation group experienced a new, non-neurological adverse event. In three participants in the neuronavigation group these events were fatal (pulmonary embolism, cardiac arrest with pulseless electrical activity, and post-operative pulmonary insufficiency).

Other adverse events included pulmonary or urinary tract infection, surgical removal of an epidural haematoma, surgical cyst drainage, repeated tumour debulking, cerebrospinal fluid leakage, post-operative delirium, and insufficiently treated steroid-induced diabetes. However, the actual numbers of each event and in what arm it occurred were not described, preventing calculation of the RR and CI.

- **Neuronavigation with DTI**: a single case of a patient dying from a 'postoperative iatrogenic pneumonia' was reported in the control arm. A single patient in each arm underwent evacuation of an 'operative field haematoma'. No wound infections were reported. Due to the low number of events, the RR and CI were not deemed appropriate.

Survival

- **iMRI**: this was not assessed.
- **5-ALA**: median survival was 15.2 months (95% CI 12.9 to 17.5) in the intervention arm versus 13.5 months (95% CI 12.0 to 14.7) in the control arm (HR 0.82, 95% CI 0.62 to 1.07).
- **Neuronavigation**: the median survival time was 9 months in the control arm and 5.6 months in the intervention arm (HR 1.6). No confidence intervals were available.
- **Neuronavigation with DTI**: subgroup analysis was presented for HGGs only; data were not presented for LGG. The median survival in the neuronavigation-DTI arm was 21.2 months (95% CI 14.1 to 28.3) versus 14.0 months (95% CI 10.2 to 17.8) in the control group (HR 0.57, 95% CI 0.32 to 1.00). Among those with only WHO grade IV tumours, survival in the neuronavigation-DTI arm was 19.3 months (95% CI 15.2 to 23.5) versus 11.1 months (95% CI 7.3 to 15.2) in the control arm (HR 0.46, 95% CI 0.24 to 0.92).

Time to progression (TTP) or progression-free survival (PFS)

- **iMRI**: median PFS in the intervention arm was 226 days (95% CI 0.0 to 454) versus 154 days (95% CI 60 to 248) in the control arm, but no HRs or their respective CIs were available.
- **5-ALA**: median PFS was 5.1 months (95% CI 3.4 to 6.0) in the intervention arm versus 3.6 months (3.2 to 4.4 months) in the control arm. HRs and their respective CIs were not available.
- **Neuronavigation**: this was not a specified outcome measure.
- **Neuronavigation with DTI**: this was not a specified outcome measure.

Quality of life (QoL)

- **iMRI**: this was not assessed.
- **5-ALA**: this was not assessed.
- **Neuronavigation**: QoL questionnaires at three month post-operatively were completed by 19 patients (8 in the neuronavigation arm and 11 in the standard surgery arm) comprising 64.5% of all eligible patients. The questionnaire included one part of 30 general questions and another part of 20 brain-specific questions (BN-20). Out of 26 outcome measures that were presented, the direction of change differed in 7 (all in the BN-20 group): 4 were in favour of the neuronavigation group and 3 were in favour of standard surgery. No statistical analysis was presented.
- **Neuronavigation with DTI**: this was not assessed.

DISCUSSION

Summary of main results

We included one RCT for iMRI (Senft 2011), one for fluorescent guided surgery with 5-ALA (Stummer 2006), and two studies with neuronavigation using both standard (Willems 2006) and diffusion tensor imaging (DTI)-based tractography (Wu 2007) pre-operative MRI sequences. Formal meta-analysis was not possible due to the variability in the control arm population between trials (that is there was variable utilisation of neuronavigation) and the baseline patient characteristics. We were, therefore, limited to performing a descriptive analysis of the included trials.

Apart from standard neuronavigation (Willems 2006), all the trials demonstrated an individual benefit for the particular method of intra-operative imaging that was assessed in terms of extent of resection (our primary outcome). Overall survival data were available for 5-ALA and DTI-neuronavigation; there was no clear evidence that these interventions improved overall survival.

Data for PFS were also only available for two trials, and were not available in the format that we had pre-specified (HRs and their variance). Nevertheless, there was a suggestion from the individual trial results that 5-ALA increased PFS compared with standard surgery. Quality of life (QoL) data has only been reported in a single trial, and on that occasion there was significant attrition and reporting bias. Adverse event reporting varied considerably between trials too. With 5-ALA, it appears that neurological deterioration is more common after fluorescence guided surgery. In the reported studies it was noted that this effect was mainly among those with fixed deficits and occurred early but then the patients recovered (Stummer 2006). However, we were unable to test these findings due to a lack of available data. Other adverse events appeared to be rare and similar in frequency between arms.

Overall completeness and applicability of evidence

All the identified trials included highly selected participants in specialised centres and the applicability of these findings to a more general population needs to be carefully considered. Our table of external validity classifies the randomised participants as generally

being young and of good performance status (Table 5). In addition, most trials also specified clearly the types of tumours that were to be included, and would not have randomised those patients with highly eloquent tumours or where a complete resection was not feasible. It is suspected that those enrolled in the iMRI trial (Senft 2011) were likely to have more resectable and have less eloquent tumours than those in the 5-ALA trial (Stummer 2006) given the far higher resection rates in both arms of the iMRI study (96% iMRI and 68% control versus 65% 5-ALA and 36% control).

The majority of the trials only enrolled participants with probable HGG. A single trial also included LGG (Wu 2007). There were no identified trials for any of the other pre-specified tumour subgroups we sought to include (specifically pituitary tumours and skull base tumours). The benefit of intra-operative imaging in these groups therefore remains undefined and our results cannot be generalised to these other tumour groups.

No RCTs were identified for ultrasound guided surgery, which may reflect the less widespread application of particularly 3D technology (such as Sonowand^{TM}). Theoretically there are many advantages to this technology such as relative affordability; repeatability; and possibly better sensitivity in low grade tumours than the other intra-operative imaging modalities that were included. Nevertheless, currently it does not have the same evidence base as other intra-operative imaging modalities with which to recommend its use in routine clinical practice.

Quality of the evidence

Clearly it is feasible to perform RCTs for new surgical interventions, and it appears now to have become de rigueur to perform an RCT for assessing novel intra-operative imaging modalities. The openness of major centres to enrolling participants in RCTs to provide clear outcome data is a major step forward in neuro-oncology. Methodological quality was suboptimal in some aspects, but for other aspects (such as blinding of radiologists in assessing extent of resection) it was good (Table 4).

Extent of resection was the primary outcome for all of the studies. This has the advantage of being the outcome most directly influenced by intra-operative imaging. However, there is still no evidence from RCTs that resection (either total or less than total) improves outcomes for HGG over biopsy alone (Hart 2011). Subgroup analyses, particularly for the 5-ALA trial (Stummer 2006), have shown that those participants that have a complete resection of all contrast enhancing tumour survive for longer than those with residual tumour (Pichlmeier 2008). Studies of chemotherapy have also found that those without residual tumour survive for longer (Stupp 2005). While this is not direct evidence in favour of complete resection, but rather a post hoc non-randomised subgroup analysis, it is becoming increasingly apparent that a complete tumour resection is desirable, particularly when it can be achieved safely. Precisely how much a complete resection contributes towards the overall outcome is unclear. New methods of imaging (e.g. amino acid positron emission tomography (PET)) have found that tumours frequently extend out from the contrast enhancing margin on MRI (Miwa 2004). Therefore, the value of MRI in assessing residual tumour is questionable.

After extent of resection, studies tended to focus on PFS rather than overall survival. There are certain advantages to this in that possibly fewer participants are required and the results may be available sooner. Additionally, it may provide a more direct assessment of the effect of the primary intervention that is not confounded by subsequent therapy. However, it can be argued that overall survival should still remain the main outcome of interest. Firstly, survival is so short in HGG that the practical benefits of assessing PFS are less relevant. Secondly, assessment of PFS can be more subjective, and is critically dependent on the timing and interpretation of imaging, which can often be complicated (RANO 2010).

Quality control for surgical neuro-oncology trials is an emerging area (GNOSIS 2007). Standardisation of reporting is required to allow clear comparisons between trials in meta-analyses. Detailed reporting is required for tumour location with regard to eloquent brain; operative technique used; post-operative imaging protocol; assessment of extent of resection; and recording of adverse events (including total numbers of events, total number of participants at risk, number of participants with multiple events, severity, timing, and outcome of events that is resolution or persistence of neurological deficits).

Potential biases in the review process

Probably our main source of bias is including an RCT that was been defined by the lead author as 'a low-quality RCT' (Wu 2007). Specificially, the lead author also clarified that the randomisation methods were not strict and that study surgeons were aware of allocations prior to enrolment. Therefore, it was stated that 'bias of patient allocating was inevitable'. Unfortunately we do not have any other specific details about the trial methodology that was applied. Rather than exclude a study which has received considerable attention within the neurosurgical and neuro-oncology community on the grounds of bias, we took the opportunity to critically appraise this trial and evaluate its findings according to Cochrane methods. It is hoped that this will allow an accurate evaluation of its data and enable comparisons with other intra-operative imaging modalities.

Others may note that we have included two specific groups of technologies, those that used imaging obtained intra-operatively and those that use imaging obtained pre-operatively for use in an intra-operative manner. We feel that both methods are suitable for comparison as the goals are similar, to achieve maximal safe resection via the application of surgical technology. Clearly, the major concern with those using pre-operative imaging is the phenomenon of intra-operative brain shift, whereby anatomical localisation is affected by events that occur during surgery (e.g. anaesthesia, brain retraction, tumour resection, durotomy and cere-

brospinal fluid drainage). Theoretically imaging obtained intra-operatively can account for brain shift and allow more accurate navigation than with imaging obtained pre-operatively. In our review, we found that the single trial did not demonstrate an effect for intra-operative imaging utilising pre-operatively acquired data (Willems 2006). However, another trial utilised pre-operatively acquired imaging and found a significant benefit with intra-operative imaging (Wu 2007), suggesting that brain shift can be accommodated for depending on the individual user and patient. Notably, the majority of trials assessing intra-operative imaging were not RCTs. One might make the argument that excluding this volume of data biases our review and that it would be more appropriate to consider a Cochrane review of non-randomised studies (NRS). However, the issue of selection bias is critical, particularly in surgical trials. Participants enrolled in NRS are likely to have a better prognosis than a control population and it is impossible to accurately account for this bias without using randomisation. Therefore, it would not be clear what benefit intra-operative imaging had on the overall outcome. Meta-analysis of RCTs remains the most reliable way of assessing the benefits of specific intra-operative imaging modalities, however, NRS do also have a role to play, particularly regarding technology development and reporting of adverse events.

Another technique that is gaining popularity in neuro-oncology surgery is awake craniotomy. This is often perceived as a technology to make surgery safer by allowing intra-operative mapping of eloquent brain. However, it can also be used to maximise extent of resection, particularly in LGG. Supra-maximal resections are now becoming feasible whereby resection of diffusively infiltrating tumours is continued until eloquent brain is reached (Yordanova 2011). There is debate whether such an approach is required in HGG too (Sanai 2009).

Agreements and disagreements with other studies or reviews

Currently we are not aware of any other similar reviews that compare all the different type of intra-operative imaging or other interventions to maximise the extent of resection in neuro-oncology. Currently, there are no national guidelines appraising the use of any of the technologies, for example by the National Institute for Health and Care Excellence (NICE). Many of the trials are relatively recent and appraisal is often limited to a linked editorial. In addition, many of the techniques have only been used in specialised trial centres, and real-world experience is limited.

AUTHORS' CONCLUSIONS

Implications for practice

Current evidence is of a low quality, however, intra-operative imaging modalities, particularly iMRI and 5-ALA, appear to be of benefit in maximising extent of resection in participants with HGG. Safely achieving a complete tumour resection appears desirable, although the direct benefits of intra-operative imaging on OS and PFS are less clear, and are probably confounded by post-intervention management. Neurological deterioration may be more common early on after 5-ALA; however there does not appear to be any additional long-term morbidity. Patients clearly need to be highly selected as those with persistent deficits despite steroids are at high risk of deterioration, while an ideal patient would be young, of good performance status, and have a well-defined tumour in a non-eloquent region that is amenable to safe complete resection (Table 5). Even with careful patient selection, intra-operative imaging will probably only lead to a direct benefit in one third to one half of all those where the technology is used. The evidence for DTI guided surgery and 3D ultrasound is of very low quality and non-existent, respectively, and the utilisation of these technologies in routine clinical practice is not clearly defined. Potentially, there is room for each neurosurgical unit to choose their preferred image guidance tool depending on their preferences that is additional operative time, combination use with standard neuronavigation technologies, operative experience, and one-off costs versus per patient running costs.

Implications for research

The current studies provide a limited knowledge base upon which to consider implementing such technologies. There are important questions remaining about benefit in terms of OS, PFS and the risk of adverse events. Future trials could be done with a similar design to those already performed but with simple improvements to the trial methodology and outcome reporting.

Sonowand^{TM} (3D ultrasound) has many theoretical advantages over other methods of neuronavigation but currently it has not been the subject of an RCT. In light of the benefits of iMRI and 5-ALA, a trial of Sonowand^{TM} would have to be in comparison with one of these established imaging modalities, or possibly in a tumour group other than HGG, such as LGG.

A direct comparison between individual intra-operative imaging modalities could be of benefit to compare their relative merits and in particular help to provide cost-effectiveness data. A comparison between iMRI and 5-ALA would be the most logical comparison but units with access to both technologies are likely to be rare and participants who are suitable for either procedure are likely to be very highly selected. Experience-based RCTs are a possible way around this. Nevertheless, there are ongoing RCTs comparing different forms of image guided surgery and these can hopefully be incorporated into an update of this review once they are completed (Ongoing studies). A network meta-analysis may allow indirect

comparisons of each technology, and an economic review could allow financial factors to be facilitated into the equation.

Assessment of intra-operative imaging modalities in other tumour groups such as pituitary and skull base tumours could be useful, but numbers may be low and recruitment difficult. The most frequent application of such technology is likely to remain those with presumed HGG.

Evidence regarding extent of resection and the means with which to achieve this is becoming stronger but this still needs to be balanced with making surgery safer. Awake craniotomy is probably the main means of enabling a maximal safe resection, particularly with tumours in eloquent areas. A comparison of DTI or functional (f)MRI guided surgery with awake craniotomy is probably the most relevant design for those with tumours in eloquent areas. In participants with tumours that aren't directly in eloquent areas the relevance of functional neuronavigation (DTI or fMRI) is less likely to be apparent.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Senft 2011

Methods	The sample size calculation was done to detect a difference of 25% between groups for the primary endpoint with a power of 80%. Randomisation was done in participants in blocks of four on a one-to-one ratio using BiAS for Windows 9.01 by an assistant who had no clinical involvement in the trial. Investigators who assessed eligibility of participants and scheduled surgeries were masked to treatment group assignment by use of a sealed envelope design. Surgeons and participants were not masked to the treatment group assignment, but the neuroradiologist who analysed MRI data was masked
Participants	Adults (≥18 years) with known or suspected gliomas showing distinct contrast enhancement on T1- weighted MRI amenable to radiologically complete resection were eligible. Exclusion criteria were: presence of cardiopulmonary or hepatorenal co-morbidities; tumours that crossed the midline or were located in the basal ganglia, cerebellum, brain stem, or otherwise in close proximity to eloquent brain structures prohibiting or questioning complete resectability; contraindications to MRI examination (eg, pacemaker); and inability to give consent because of neuropsychological deficits or a language barrier
Interventions	In intervention consisted of mobile intra-operative ultralow field (015 Tesla) MRI system (PoleStar N-20, Odin Medical Technologies, Yokneam, Israel and Medtronic, Louisville, CO, USA)13,14 for procedures guided by intra-operative MRI. The control arm used 'conventional micro neurosurgical resection' including CUSA and neuronavigation. The use of intra-operative ultrasound or fluorescence guided surgery with 5-aminolaevulinic acid was not allowed in either group
Outcomes	The primary endpoint was extent of resection. All participants underwent high-field MRI at 1·5 T or 3·0 T with and without contrast agent within 7 days before surgery and within 72h after surgery. One masked, independent, and experienced neuroradiologist (AB) assessed MRIs to establish the extent of resection and undertake volumetric analyses of the tumours and tumour residues. Residual tumour was defined as detectable contrast enhancement on T1-weighted imaging with a volume of more than 0·175 cm^3 on post-operative MRI as done previously Secondary endpoints were the volume of residual tumour on post-operative MRI and progression-free survival (PFS) at 6 months. We also compared the duration of surgery and treatment-related morbidity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done in participants in blocks of four on a one-to-one ratio using BiAS for Windows 9.01 by an assistant who had no clinical involvement in the trial

Senft 2011 (*Continued*)

Allocation concealment (selection bias)	High risk	Sealed envelope design
Blinding of participants and personnel (performance bias) All outcomes	High risk	Surgeons and participants were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Only the neuroradiologist analysing the MRI data was blinded which is important for assessing extent of resection. Assessors of clinical outcomes were not masked, which would have affected progression-free survival and treatment-related morbidity
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	49 of 58 participants analysed (4 excluded in each arm because of the diagnosis of a metastasis and 1 withdrew consent in the iMRI arm)
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported (extent of resection, residual tumour volume, PFS and treatment-related morbidity)
Other bias	High risk	The study was stopped early due to an interim analysis resulting in a reduced sample size from 80 to 58. Due to the possible effect of this adjustment on the alpha error and to avoid over interpretation of the data, a P value of less than 0·04 was considered significant for the primary endpoint No external funding source for the study declared but it was noted in an earlier abstract that one of the authors received an honorarium from Medtronic who manufacture the scanner

Stummer 2006

Methods	Randomisation was done by use of a dynamic allocation algorithm at a separate research unit, in which participants were allocated to keep the imbalance between treatment groups to a minimum. No permuted block randomisation was applied. Treatment allocation was communicated to local investigators first by telephone and additionally by fax Initial power calculations estimated 350 participants were required for an 80% power but to allow premature study termination an interim analysis was scheduled after 270 participants whereby a 20\5 difference in PFS could be identified with a power of 80%

Participants	Inclusion criteria: participants aged 18-72 y with suspected (as assessed by study surgeon) newly diagnosed intreated malignant glioma. Tumours were to have a distinct ring-like pattern of contrast enhancement with thick irregular walls on MRI and a core area of reduced signal suggestive of tumour necrosis Exclusion criteria: tumours in the midline, basal ganglia, cerebellum or brain stem; more than one contrast enhancing lesion; substantial, non-contrast enhancing tumour with areas suggesting low grade glioma with malignant transformation; medical reasons precluding MRI; inability to give consent; a tumour location that did not enable complete resection; KPS of 60 or less; renal or liver insufficiency; and a history of previous systemic malignancy
Interventions	Participants were randomly assigned to 5-aminolevulinic acid (20 mg/kg bodyweight; medac, Wedel, Germany) for fluorescence guided resection or to conventional micro-surgery with white light. Those randomly allocated to 5-aminolevulinic acid were scheduled to receive freshly prepared solutions of 5-aminolevulinic acid orally 3h (range 2 - 4) pre-operatively. Solutions were prepared by dissolving the contents of a vial (1·5g) in 50 mL of drinking water. There was no placebo Surgery was done by use of a modified neurosurgical microscope (OPMI Neuro/NC4 system with fluorescence kit, Carl Zeiss Surgical GmbH, Oberkochen, Germany), which enabled switching from conventional white xenon illumination to violet-blue excitation light. For participants assigned white light, the tumour was resected by use of conventional illumination
Outcomes	Primary endpoints: complete tumour resection on MRI (<72 hours post-operation and >1.5 Tesla) and PFS Secondary endpoints: residual tumour volume, overall survival, type and severity of neurological deficits after surgery, and toxic effects Follow-up was at 6 weeks then 3 months and subsequently at 3 monthly intervals until 18 months
Notes	Residual tumour was defined as contrast enhancement with a volume more than 0·175 cm^3. Progression was defined as the occurrence of a new tumour lesion with a volume greater than 0·175 cm^3, or an increase in residual tumour volume of more than 25%. Progression-free survival was defined radiologically in the initial trial and by combined measures in the follow-up paper (radiological criteria as above plus any new tumour or neurological worsening as defined by an NIH-SS score increase over 1) Adverse events were classified according to the US National Cancer Institute common toxicity criteria (version 1.0) The US National Institutes of Health stroke score (NIH-SS) was used to measure post-operative deficits at 2 and 7 days after surgery, radiological progression at 6 weeks, then at 3, 6, 9, 12, 15 and 18 months post-surgery Inter-centre consistency was not presented. The manufacturer of 5-ALA (medac GmbH) was involved with the trial and authors had received assistance from the sponsor
Risk of bias	

Stummer 2006 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Performed independently with a dynamic allocation algorithm
Allocation concealment (selection bias)	Low risk	Treatment allocation was communicated by telephone and fax
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no blinding for surgeons, participants or those involved with treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Neuropathology and neuroradiological assessments were blinded, which is important for assessing extent of resection. Clinical outcome assessment was not blinded, which would have affected progression-free survival and adverse events
Incomplete outcome data (attrition bias) All outcomes	High risk	13 participants excluded for major violations of MRI inclusion criteria. 34 participants excluded for histological criteria. In total out of 322 randomly assigned 270 were analysed ITT and 251 per protocol
Selective reporting (reporting bias)	High risk	Full outcome data were not presented for survival, PFS and AEs (particularly in the earlier article but less so in the follow-up paper). For example Kaplan-Meier plots with HR, 95% CI and log-rank analyses for the full cohort were not present for survival, PFS (no HR with 95% CI) or time to deteriorate in the NIH-SS (subgroup only of those with complete resection). Timing and severity of all AEs were not fully documented (for example, there is no data on wound infections or related complications and medical complications such as pulmonary thromboembolism)
Other bias	Unclear risk	Although the sponsor was heavily involved with the study it was emphasised there was no direct link with data interpretation, however certain authors had also received remuneration from the sponsor too

Willems 2006

Methods	Based on the results of a power analysis (details not specified in the paper) the authors planned to include 182 participants in the study, but the trial was stopped at 45 participants after an early pilot analysis. The participants were stratified by age (< 45 or ≥ 45) and KPS (≤ 70 or > 70), and they were evenly randomized to SS (without neuronavigation) or SN (with neuronavigation) by using a computer-generated list with allocation codes in random order, balanced for each stratum using blocks of four. There was no blinding
Participants	It included participants harbouring a solitary intracerebral space-occupying lesion with (partial) contrast enhancement that were eligible for surgical debulking with the intention of gross total resection (GTR). It excluded participants who had a previous neurosurgical treatment or any other known primary tumour elsewere in the body
Interventions	Neuronavigation was performed with bone fiducial markers. Pre-operative MR images were obtained using a 0.5 tesla system with contrast enhanced T1 weighted images. Volumetric measurements were performed to assess total lesion volume. Functional grading was recorded according to the MD Anderson scheme (Sawaya 1998). Planning involved localisation using fiducial markers, trajectory planning and segmentation of the tumour boundary. Tools included an infrared pointer or mechanically tracked operating microscope
Outcomes	Post-operative MR images were obtained within 72 hours and subject to volumetric analysis. Post-operative clinical assessment was performed post-operatively within 3 days, 1 week, 6 weeks and 3 months to assess adverse events and neurological status (using KPS and BI scores). A QoL questionnaire (EORTC QLQ-C30 and BR-20) was filled out pre-operatively and approximately 3 months after surgery. The primary outcome was extent of resection and survival. Other outcomes were procedure duration, usefulness of neuronavigation, extent of resection, QoL and post-operative course (including neurological status and adverse events)
Notes	There were 3 early deaths in the navigation arm from systemic causes, which with the low numbers in each arm skewed the results. The trial was stopped early

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The participants were randomized to SS (without neuronavigation) or SN (with neuronavigation) by using a computer-generated list with allocation codes in random order, balanced for each stratum using blocks of four. However, groups were not evenly distributed at baseline with regard to more eloquently located tumours in the standard surgery arm and histology with more metastasis in the navigation arm (although the latter was a variable not able to be determined pre-operatively

Willems 2006 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	1 patient was excluded due to an alternative diagnosis (meningioma). Post-operative imaging was only assessed in 34/45 participants for tumour volume and 40/45 for contrast enhancing volume. Data for QoL at 3 months was only reported on 64.5% of the total eligible population
Selective reporting (reporting bias)	High risk	All outcomes measures were reported to a degree. However full data with suitable presentation and analysis were not available for survival (no Kaplan-Meier plots), QoL (no statistical analysis) and adverse events (no presentation of numbers of events)
Other bias	High risk	The trial was significantly underpowered and terminated prematurely. Out of 280 potentially eligible participants only 46 participants were included, with a planned target of 182

Wu 2007

Methods	Power calculation and randomizstion technique were not stated. The peri-operative evaluation regarding age, sex, lesion location, tumour volume, initial motor function, final histological diagnosis, navigational predicted accuracy value as well as post-operative motor function and surgical complications was conducted by both the resident neurosurgeon and the operating neurosurgeon. They were members of the treatment team and were not blinded to the treatment strategies. The early post-operative imaging assessment was performed by independent neuroradiologists who were blinded to the treatment strategies
Participants	The inclusion criteria defined the participants who were aged 6 to 75 years with an initial imaging diagnosis of single, unilateral, supratentorial primary glioma. The lesions were involved in pyramidal tracts (PTs) comprising cortical regions in the motor or somatosensory areas, cortical regions adjacent to the central gyrus, subcortical regions with an infiltrative progression along the PTs, and temporal or insular regions in relation to the internal capsule. No contraindications for MRI were present. The exclusion criteria

	were as follows: participants with secondary or recurrent gliomas, participants with contraindications for MRI, and participants for whom initial muscle strength grade of the affected extremities was 0/5 (no contraction at all)
Interventions	The control arm included those participants who underwent craniotomies using neuronavigational guidance with the routine 3-D navigational MRI data set only. The study arm included participants to be examined by DTI for PT mapping and who later underwent operations using neuronavigation with the co-registered data sets of both 3-D navigational MRI and functional anisotropy (FA) maps of DTI. Images were acquired with either a 1.5 or 3.0 tesla MR scanner using either contrast-enhanced T1 weighted or FLAIR (if no enhancement) images. The DTI was performed with single-shot spin-echo echo planar sequence and image processing completed to calculate FA maps and fiber tracking (23 participants) of the PTs. StealthStation Treon neuronavigator (Medtronic) was used image integration with StealthMerge software, Stealth station with stealth merge, iPlan cranial software
Outcomes	All procedures for the two treatment groups were analysed with respect to peri-operative results as follows: the extent of tumour resection achieved as confirmed by early post-operative MRI scans, post-operative motor function alteration of the affected extremities on discharge from the hospital, and further possible surgery-related complications (e.g. wound infection, haematoma, cerebral infarction, etc). Early post-operative MRI with contrast enhanced T1 weighted or FLAIR images within 3 days post-operatively. Gross total resection referred to no residual tumour on post-operative MRI (specifically no residual enhancement); subtotal resection was 10% residual; partial resection was greater than 10% residual. Survival and functional status were assessed by two independent but non-blinded neurosurgeons
Notes	24 of 238 excluded Median follow-up of 21.3 months (maximum 50.5 months) Follow-up of LGG at 3 months then 6 monthly intervals

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Stated via e-mail correspondence to be 'not strict'
Allocation concealment (selection bias)	High risk	Stated via email correspondence that investigators were not blinded with the implication that they were aware of post-randomisation allocation and therefore there was an accepted bias in enrolment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded

Wu 2007 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	The members of the treatment team and were not blinded to the treatment strategies. The early post-operative imaging assessment was performed by independent neuroradiologists who were blinded to the treatment strategies
Incomplete outcome data (attrition bias) All outcomes	High risk	A degree of attrition bias was apparent for each outcome including extent of resection, survival and adverse events. Analysis was not intention to treat with a significant proportion excluded due to protocol violations and loss to follow-up. A flow diagram was not presented to describe attrition
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes of interest were reported (extent of resection, survival and adverse events)
Other bias	Unclear risk	-

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

Study	Reason for exclusion
Bergsneider 2005	Participants were not randomised. Retrospective study
Eljamel 2008	The addition of PDT (repetitive photodynamic therapy) essentially precludes analysis of this trial as a test of intra-op imaging alone. Therefore it was excluded
Koc 2008	Participants were not randomised. Prospective study
Rhode 2011	This trial was assessing specificity and sensitivity of intra-operative 3-D ultrasound as diagnostic test rather than treatment option
Wirtz 2000	Participants undergoing resection as primary treatment for gliomblastoma multiforme using neuronavigation were matched retrospectively with a similar group undergoing surgery without neuronavigation. Therefore there was not a prospective random allocation process between treatment arms and the trial methodology did not meet our inclusion criteria
Wu 2003	Author stated this was not a randomised controlled trial
Wu 2004	Author stated this was not a randomised controlled trial

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

NCT00752323

Trial name or title	Imaging Procedure Using ALA in Finding Residual Tumor in Grade IV Malignant Astrocytoma
Methods	'Randomised' - possibly diagnostic only trial design
Participants	Newly diagnosed and recurrent grade IV glioma
Interventions	2 doses of 5-ALA
Outcomes	In-vivo and pathological fluorescence Extent of resection (possibly - not clear from trial notes)
Starting date	August 2008
Contact information	Andrew Sloan
Notes	Case Medical Centre, Cleveland, Ohio, USA.

NCT00943007

Trial name or title	Comparison of Standard Neuronavigation With Intraoperative Magnetic Resonance Imaging (MRI) for the Neurosurgical Treatment of Malignant Brain Tumors
Methods	Randomised. Single blind (outcome assessors)
Participants	Newly diagnosed suspected GBM on imaging suitable for gross total resection. Age over 18 years. WHO performance status 0-2
Interventions	Intra-operative MRI (PoleStar N20). Stealth Station
Outcomes	Difference in residual tumour volume <72 hours after surgery
Starting date	February 2010
Contact information	Kubben PL
Notes	Maastricht University Medical Center, Belgium

NCT00977327

Trial name or title	Comparison of Neuronavigational Systems for Resection-Control of Brain Tumors
Methods	Randomised trial
Participants	Neuroradiological evidence of a brain lesion

NCT00977327 (*Continued*)

Interventions	Intra-operative MR (Polestar N-20) versus intra-operative ultrasound (Sonowand)
Outcomes	Extent of resection Cost-effectiveness
Starting date	2009
Contact information	Andrew Kanner
Notes	Tel Aviv, Israel

NCT01479686

Trial name or title	iMRI Guided Resection in Cerebral Glioma Surgery
Methods	Randomised. Phase III. Single blind (outcome assessor)
Participants	Newly diagnosed malignant glioma. Age 18-70. Karnofsky performance score 70-100. Supratentorial tumours
Interventions	Intra-operative MRI (3 tesla)
Outcomes	Extent of resection Progression-free Survival Overall survival Post-operative complications Health economics
Starting date	September 2011
Contact information	Zhou L-F, Mao Y, Wu J-S
Notes	Huashan Hospital, Shanghai, China

NCT01502280 (BALANCE)

Trial name or title	Fluorescence-guided Surgery for Low- and High-grade Gliomas
Methods	Randomised. Single blind
Participants	Newly diagnosed glioma (high and low grade)
Interventions	5-ALA/Gliolan versus placebo (ascorbic acid)
Outcomes	1. Volume of residual disease 2. Overall survival 3. 6-month progression-free survival

NCT01502280 (BALANCE) (*Continued*)

Starting date	November 2010
Contact information	Nader Sanai (principal investigator), Norissa Honea (overall contact)
Notes	Barrow, Phoenix, Arizona, USA

NCT01798771

Trial name or title	Intraoperative MRI and 5-ALA Guidance to Improve the Extent of Resection in Brain Tumor Surgery (IMAGER)
Methods	Randomised
Participants	Newly diagnosed supratentorial intra-axial brain tumour suspicious for malignant glioma. Deemed resectable
Interventions	Intervention: 5-ALA and intra-operative MRI Control: 5-ALA
Outcomes	1. Extent of resection (according to post-operative MRI within 72 hours) 2. Volumetric extent of resection 3. Progression-free survival 4. Quality of life 5. National Institutes of Health Stroke Scale (NIHSS)
Starting date	February 2013
Contact information	Christian Senft
Notes	Johann Wolfgang Goethe University Hospitals, Germany

DATA AND ANALYSES

Comparison 1. Image guided surgery versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incomplete resection (HGG)	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 iMRI	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 5-ALA	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 DTI-neuronavigation	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Image guided surgery versus control, Outcome 1 Incomplete resection (HGG).

Review: Image guided surgery for the resection of brain tumours

Comparison: 1 Image guided surgery versus control

Outcome: 1 Incomplete resection (HGG)

Study or subgroup	Image guided surgery n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 iMRI				
Senft 2011	1/24	8/25		0.13 [0.02, 0.96]
2 5-ALA				
Stummer 2006	49/139	84/131		0.55 [0.42, 0.71]
3 DTI-neuronavigation				
Wu 2007	10/42	29/43		0.35 [0.20, 0.63]

ADDITIONAL TABLES

Table 1. Data extraction pro forma

Methods, internal validity and risk of bias	Data output from trial
Power calculation	
Eligibility criteria stated	
Random sequence generation	
Allocation concealment	
Blinding	
Groups comparable at baseline	
Objective outcome data	
Selective reporting	
ITT analysis	
Inter-centre consistency	
Conflict of interest	
Participants	
Primary or recurrent therapy	
Tumour histology	
WHO score	
Tumour location	
Contrast enhancement	
Age (mean and range)	
Performance status (KPS)	
Gender split	
Interventions	
Control arm: extent of surgery, dose of radiation, use of chemotherapy	

Table 1. Data extraction pro forma (*Continued*)

Intervention arm: above plus type of intervention (see below)	
5-ALA: dose and timing, timing of ultraviolet light intra-operatively, microscope used	
Additionally, the surgical decision-making influenced by the intra-operative imaging should be stated	
Outcomes and data abstraction	
Numbers per arm	
Extent of resection (numbers, RR an CI)	
Survival: HR and log variance	
Progression-free survival: HR and log variance	
Quality of life data: number at risk, value and SD	
Adverse events: number at risk and relative risk	

Table 2. Karnofsky Performance Score

Score	Definition
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity: minor symptoms of disease
80	Normal activity with effort: some symptoms of disease
70	Cares for self: unable to carry on normal activity or active work
60	Requires occasional assistance but is able to care for needs
50	Requires considerable assistance and frequent medical care
40	Disabled: requires special care and assistance
30	Severely disabled: hospitalisation is indicated, death not imminent
20	Very sick, hospitalisation necessary: active treatment necessary
10	Moribund, fatal processes progressing rapidly

Table 2. Karnofsky Performance Score (*Continued*)

0	Dead

Table 3. WHO Performance Score

Grade	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work
2	Ambulatory and capable of all self care, but unable to carry out ay work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair
5	Dead

Table 4. Internal validity

	Senft 2011	Stummer 2006	Willems 2006	Wu 2007
Power calculation	Yes	Yes	Yes	Not stated
Randomisation methods	Good	Good	Good	Poor
Stratification at randomisation	No	Minimisation technique	Minimisation technique	No
Allocation concealment	Unclear	Yes	Not stated	No
Inclusion/exclusion criteria stated	Yes	Yes	Yes	Yes
Group similarity at baseline	Yes	Yes	No	Yes
Outcome assessment blinded	Some	Some	No	Some
Investigators blinded	No	No	No	No
Participants blinded	No	No	No	No

Table 4. Internal validity (*Continued*)

Objective outcome criteria	Some	Some	Some	Some
ITT analysis	No	No	No	No
Protocol deviations	Yes	Yes	Yes	Not stated
All participants accounted for	Yes	Yes	No	No
Withdrawals specified	Yes	Yes	Yes	No
Withdrawal reasons given	Yes	Yes	Yes	No
Inter-centre consistency	Single centre	Not stated	Single centre	Single centre
Conflict of interest	Possibly	Possibly	Not stated	Not stated

ITT: intention-to-treat

Table 5. External validity

	Senft 2011	Stummer 2006	Willems 2006	Wu 2007
Age (median and range)	iMRI: 55.3 (38-76) Control: 55.0 (30-84)	5-ALA: 61 (23-73) Control: 60 (30-73)	Neuronavigation: 60.6 (SD 12.1) Control: 60.8 (SD 12.1)	Neuronavigation: 40.8 (6-75) Control: 38.0 (6-70)
Sex (M:F)	iMRI: 67:33 Control: 56:44	5-ALA: 58:42 Control: 64:36	Neuronavigation: 26:74 Control: 36:64	Neuronavigation: 66:34 Control: 65:35
Performance score	iMRI: KPS 90 (60-100) Control: KPS 90 (70-100)	5-ALA: 90 (60-100) Control: 90 (70-100)	Neuronavigation: 77.4 (SD 19.4) Control: 78.6 (SD 15.5)	KPS at baseline not stated.
Histology	iMRI: 22 WHO IV; 1 WHO III; 1 WHO I Control: 24 WHO IV; 1 WHO III	5-ALA: 97.2% WHO IV; 2.9% WHO III Control: 96% WHO IV; 3.5% WHO III	Neuronavigation: 3 anaplastic, 15 GBM, 5 metastasis Control: 5 anaplastic, 16 GBM, 1 metastasis	Neuronavigation: WHO I 0.8%, WHO II 49.9%, WHO III 12.7%, WHO IV 37.3%, Nonglioma 11.9% Control: WHO I 4.1%, WHO II 50.9%, WHO III 17.5%, WHO IV 19.%, Nonglioma 8.3%

Table 5. External validity (*Continued*)

Tumour locations	Not specified	5-ALA: eloquent 56.3% Control: eloquent 54. 3%	Neuronavi- gation: 8 ACC I, 7 ACC II, 4 ACC III Control: 7 ACC I, 7 ACC II, 8 ACC III	All involving the pyrami- dal tracts (PTs)
Tumour enhancement	Defined in inclusion cri- teria	Defined in inclusion cri- teria	Neuronavigation: 37.9* (SD 27.6) Control: 33.6* (SD 26. 6)	Neuronavigation: 0.581 to 321.725** cm3 (me- dian, 24.101 cm3) Control: 0.272 cm3 to 233.761** cm3 (me- dian, 21.371 cm3)
Intervention	intra-operative (i)MRI (0.15 Tesla)	5-aminolevulinic acid (5-ALA)	Neuronavigation	Neuronavigation with DTI
Control arm	neuronavigation but not ultrasound or 5-ALA	neuronav- igation for planning and localisation only	neurosurgery without any image guidance	neuronavigation without DTI
Definitions	Residual tumour only. No definitions for PFS or adverse events	Residual tumour; PFS, AE; neurological deficits (NIH-SS)	Residual tumor only. No definitions for adverse events.	Residual tumour only. No definition for adverse events.
Follow-up	Not stated	35.4 months (1.0-56.7)	3 months	Median 21.3

ACC: Anderson Cancer Center grade (ACC Grade I, non-eloquent brain; Grade II near eloquent brain; and Grade III, eloquent brain)
*Volume of contrast enhancement tumour in cm^3.
**Volume of tumour in cm^3

APPENDICES

Appendix 1. WHO Classification of CNS Tumours

TUMOURS OF NEUROEPITHELIAL TISSUE

- **Neuronal and mixed neuronal-glial tumours**
  - **Astrocytic tumours**
    - ◇ Pilocytic astrocytoma
    - ◇ Pilomyxoid astrocytoma
    - ◇ Subependymal giant cell astrocytoma
    - ◇ Pleomorphic xanthoastrocytoma
    - ◇ Diffuse astrocytoma
    - ◇ Fibrillary astrocytoma
    - ◇ Gemistocytic astrocytoma

- ◇ Protoplasmic astrocytoma
- ◇ Anaplastic astrocytoma
- ◇ Glioblastoma
- ◇ Giant cell glioblastoma
- ◇ Gliosarcoma
- ◇ Gliomatosis cerebri

○ **Oligodendroglial tumours**

- ◇ Oligodendroglioma
- ◇ Anaplastic oligodendroglioma

○ **Oligoastrocytic tumours**

- ◇ Oligoastrocytoma
- ◇ Anaplastic oligoastrocytoma

○ **Ependymal tumours**

- ◇ Subependymoma
- ◇ Myxopapillary ependymoma
- ◇ Ependymoma
- ◇ Cellular Papillary Clear cell Tanycytic
- ◇ Anaplastic ependymoma

○ **Choroid plexus tumours**

- ◇ Choroid plexus papilloma
- ◇ Atypical choroid plexus papilloma
- ◇ Choroid plexus carcinoma

○ **Other neuroepithelial tumours**

- ◇ Astroblastoma
- ◇ Chordoid glioma of the third ventricle
- ◇ Angiocentric glioma

○ **Neuronal and mixed neuronal-glial tumours**

- ◇ Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)
- ◇ Desmoplastic infantile astrocytoma/ ganglioglioma
- ◇ Dysembryoplastic neuroepithelial tumour
- ◇ Gangliocytoma
- ◇ Ganglioglioma
- ◇ Anaplastic ganglioglioma
- ◇ Central neurocytoma
- ◇ Extraventricular neurocytoma
- ◇ Cerebellar liponeurocytoma
- ◇ Papillary glioneuronal tumour
- ◇ Rosette-forming glioneuronal tumour of the fourth ventricle
- ◇ Paraganglioma

○ **Tumours of the pineal region**

- ◇ Pineocytoma
- ◇ Pineal parenchymal tumour of intermediate differentiation
- ◇ Pineoblastoma
- ◇ Papillary tumour of the pineal region

○ **Embryonal tumours**

- ◇ Medulloblastoma
- ◇ Desmoplastic/nodular medulloblastoma
- ◇ Medulloblastoma with extensive nodularity
- ◇ Anaplastic medulloblastoma
- ◇ Large cell medulloblastoma
- ◇ CNS primitive neuroectodermal tumour
- ◇ CNS Neuroblastoma

- ◇ CNS Ganglioneuroblastoma
- ◇ Medulloepithelioma
- ◇ Ependymoblastoma
- ◇ Atypical teratoid / rhabdoid tumour

Appendix 2. Search strategies

CENTRAL

#1 MeSH descriptor Central Nervous System Neoplasms explode all trees
#2 ((central nervous system or CNS) near/5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or metastat* or malignan*))
#3 ((brain or intracranial or intra-cranial or cerebr*) near/5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or metastat* or malignan*))
#4 MeSH descriptor Neoplasms, Neuroepithelial explode all trees
#5 (glioma* or astrocytoma* or xanthoastrocytoma* or glioblastoma* or gliosarcoma* or oligodendrogli* or oligoastrocyt* or ependym* or subependym* or astroblastoma* or gangliogliomа* or gangliocytoma* or neurocytoma* or liponeurocytoma* or pineocytoma* or pineoblastoma* or medulloblastoma* or neuroblastoma* or ganglioneuroblastoma*or medulloepithelioma*)
#6 ((glioneural or neuroectodermal or embryonal or neuroepithelial or pineal or choroid plexus or teratoid or rhabdoid) near/5 (tumor* or tumour*))
#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)
#8 MeSH descriptor Fluorescence, this term only
#9 MeSH descriptor Aminolevulinic Acid, this term only
#10 fluorescen*
#11 (aminolevulinic acid or 5-aminolevulinic acid)
#12 ALA
#13 MeSH descriptor Magnetic Resonance Imaging explode all trees
#14 (MRI or magnetic resonance imag*)
#15 MeSH descriptor Ultrasonography explode all trees
#16 (ultrasound or ultrasonography)
#17 3D
#18 MeSH descriptor Neuronavigation, this term only
#19 MeSH descriptor Surgery, Computer-Assisted, this term only
#20 (navigat* or neuronavigat* or neuro-navigat*)
#21 ((intra-operative or intraoperative) near/5 (technolog* or modalit*))
#22 (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21)
#23 (#7 AND #22)

MEDLINE Ovid

1 exp Central Nervous System Neoplasms/
2 ((central nervous system or CNS) adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or metastat* or malignan*)).mp.
3 ((brain or intracranial or intra-cranial or cerebr*) adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or metastat* or malignan*)).mp.
4 exp neoplasms, neuroepithelial/
5 (glioma* or astrocytoma* or xanthoastrocytoma* or glioblastoma* or gliosarcoma* or oligodendrogli* or oligoastrocyt* or ependym* or subependym* or astroblastoma* or gangliogliomа* or gangliocytoma* or neurocytoma* or liponeurocytoma* or pineocytoma* or pineoblastoma* or medulloblastoma* or neuroblastoma* or ganglioneuroblastoma*or medulloepithelioma*).mp.
6 ((glioneural or neuroectodermal or embryonal or neuroepithelial or pineal or choroid plexus or teratoid or rhabdoid) adj5 (tumor* or tumour*)).mp.
7 1 or 2 or 3 or 4 or 5 or 6
8 Fluorescence/
9 Aminolevulinic Acid/
10 fluorescen*.mp.
11 (aminolevulinic acid or 5-aminolevulinic acid).mp.
12 ALA.mp.

13 exp Magnetic Resonance Imaging/
14 (MRI or magnetic resonance imag*).mp.
15 exp Ultrasonography/
16 (ultrasound or ultrasonography).mp.
17 3D.mp.
18 Neuronavigation/
19 Surgery, Computer-Assisted/
20 (navigat* or neuronavigat* or neuro-navigat*).mp.
21 ((intra-operative or intraoperative) adj5 (technolog* or modalit*)).mp.
22 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23 7 and 22
24 randomized controlled trial.pt.
25 controlled clinical trial.pt.
26 randomized.ab.
27 placebo.ab.
28 clinical trials as topic.sh.
29 randomly.ab
30 trial.ti.
31 24 or 25 or 26 or 27 or 28 or 29 or 30
32 23 and 31
33 exp animals/ not humans.sh.
34 32 not 33
key:
mp = protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier
pt = publication type
ab = abstract
ti = title

EMBASE Ovid

1 exp central nervous system tumor/
2 ((central nervous system or CNS) adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or metastat* or malignan*)).mp.
3 ((brain or intracranial or intra-cranial or cerebr*) adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or metastat* or malignan*)).mp.
4 neuroepithelioma/
5 (glioma* or astrocytoma* or xanthoastrocytoma* or glioblastoma* or gliosarcoma* or oligodendrogli* or oligoastrocyt* or ependym* or subependym* or astroblastoma* or ganglioglioma* or gangliocytoma* or neurocytoma* or liponeurocytoma* or pineocytoma* or pineoblastoma* or medulloblastoma* or neuroblastoma* or ganglioneuroblastoma*or medulloepithelioma*).mp.
6 ((glioneural or neuroectodermal or embryonal or neuroepithelial or pineal or choroid plexus or teratoid or rhabdoid) adj5 (tumor* or tumour*)).mp.
7 1 or 2 or 3 or 4 or 5 or 6
8 exp fluorescence/
9 aminolevulinic acid/
10 fluorescen*.mp.
11 (aminolevulinic acid or 5-aminolevulinic acid).mp.
12 ALA.mp.
13 exp nuclear magnetic resonance imaging/
14 (MRI or magnetic resonance imag*).mp.
15 exp echography/
16 (ultrasound or ultrasonography).mp.
17 3D.mp.
18 neuronavigation/
19 computer assisted surgery/
20 (navigat* or neuronavigat* or neuro-navigat*).mp.

21 ((intra-operative or intraoperative) adj5 (technolog* or modalit*)).mp.
22 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23 7 and 22
24 crossover procedure/
25 double-blind procedure/
26 randomized controlled trial/
27 single-blind procedure/
28 random*.mp.
29 factorial*.mp.
30 (crossover* or cross over* or cross-over*).mp.
31 placebo*.mp.
32 (double* adj blind*).mp.
33 (singl* adj blind*).mp.
34 assign*.mp.
35 allocat*.mp.
36 volunteer*.mp.
37 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38 23 and 37
key:
[mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

WHAT'S NEW

Last assessed as up-to-date: 2 March 2013.

Date	Event	Description
21 September 2016	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 3, 2012

Review first published: Issue 1, 2014

Date	Event	Description
1 April 2015	Amended	Contact details updated.
11 February 2015	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

Damiano G Barone wrote the draft review.

Michael G Hart conceptualised the review, performed the statistical analysis, and completed the final drafting of the review.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- None, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None declared

NOTES

Nil

INDEX TERMS

Medical Subject Headings (MeSH)

Aminolevulinic Acid; Brain Neoplasms [*surgery]; Glioma [*surgery]; Magnetic Resonance Imaging, Interventional; Neuronavigation [methods]; Randomized Controlled Trials as Topic; Surgery, Computer-Assisted [*methods]

MeSH check words

Humans