Cochrane Library

Cochrane Database of Systematic Reviews

Intraoperative imaging technology to maximise extent of resection for glioma (Protocol)

Jenkinson MD, Barone DG, Hart MG, Bryant A, Lawrie TA, Watts C

Jenkinson MD, Barone DG, Hart MG, Bryant A, Lawrie TA, Watts C.
Intraoperative imaging technology to maximise extent of resection for glioma.
Cochrane Database of Systematic Reviews 2017, Issue 9. Art. No.: CD012788.
DOI: 10.1002/14651858.CD012788.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Intraoperative imaging technology to maximise extent of resection for glioma

Michael D Jenkinson[1], Damiano Giuseppe Barone[2], Michael G Hart[3], Andrew Bryant[4], Theresa A Lawrie[5], Colin Watts[3]

[1]Department of Neurosurgery, The Walton Centre NHS Foundation Trust, Liverpool, UK. [2]Department of Neurosurgery, The Walton Centre for Neurology and Neurosurgery, Liverpool, UK. [3]Academic Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrookes Hospital, Cambridge, UK. [4]Institute of Health & Society, Newcastle University, Newcastle upon Tyne, UK. [5]Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group, Royal United Hospital, Bath, UK

Contact address: Michael D Jenkinson, Department of Neurosurgery, The Walton Centre NHS Foundation Trust, Lower Lane, Liverpool, Merseyside, L9 7LJ, UK. Michael.Jenkinson@liverpool.ac.uk.

Editorial group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.
Publication status and date: New, published in Issue 9, 2017.

Citation: Jenkinson MD, Barone DG, Hart MG, Bryant A, Lawrie TA, Watts C. Intraoperative imaging technology to maximise extent of resection for glioma. *Cochrane Database of Systematic Reviews* 2017, Issue 9. Art. No.: CD012788. DOI: 10.1002/14651858.CD012788.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To establish the overall effectiveness and safety of intraoperative imaging in resection of glial tumours.

BACKGROUND

Description of the condition

Tumours of the central nervous system (CNS) constitute a large group characterised by a wide range of genetic, histological, and functional diversity (Loius 2016). Secondary brain tumours or metastases are the most common, accounting for almost half of all CNS tumours. Primary brain tumours typically occur as some variation of a glioma, so called because they arise from the supporting glial cell architecture; of these, glioblastoma is the most frequent and most malignant histological subtype (Ohgaki 2009). Brain tumours may present with headaches, neurological deficits, or seizures, alone or in combination. Treatment choices include surgery (usually biopsy or resection), radiotherapy, and chemotherapy. National guidelines recommend that management of a CNS tumour should be discussed by a multi-disciplinary team (MDT) and individually tailored to patient needs (NICE 2006).

Description of the intervention

Intraoperative magnetic resonance imaging (iMRI) involves creating a strong magnetic field, applying radiofrequency pulses, and analysing effects of this on the tissue of interest. Details on the fine anatomical structure of soft tissues provided by this technique have revolutionised the field of neuroscience, but the equipment is expensive and bulky. Intraoperative MRI requires a specific portable magnetic resonance imaging (MRI) scanner or a parallel stationary MRI scanner that is available for use in an adjacent diagnostic room. Acquisition of iMRI is aimed at providing high-definition, easily interpreted images for real-time assessment of tumour resection, allowing the possibility of immediate further resection during

the same operative session (Black 1997; Seifert 2003). Uptake has been limited by low field strength scanners, which are associated with poor image quality, extended surgical time and substantial capital costs.

Neuro-navigation refers to the computational process involved in representing a spatial position via imaging data in real time. Preoperative imaging is used to localise a lesion, perform a tailored craniotomy, and guide resection. Postoperative MRI is performed to determine the extent of resection. A major limitation of this technique is the phenomenon of intraoperative brain shift, whereby the preoperative anatomy is altered during tumour resection and accuracy is reduced. Advantages include the potential to use functional brain imaging studies to define eloquent or invaded tissues.

Ultrasonography (US), performed in two or three dimensions (2D or 3D, respectively), enables visualisation of structures through recorded reflections of echoes of ultrasonic wave pulses (frequency > 20 megahertz) directed into the tissue of interest. Freehand movement of a US probe allows determination of image volume in 3D. Volumetric reconstruction allows neuro-navigation accurate to within 1.4 mm. Updated 3D US volumes can be created at any time during surgery. Sonowand (Sonowand AS, Trondheim, Norway) is marketed as a high-quality 3D US system that offers real-time repeatable volumetric reconstruction of residual tumour. Advantages include relative affordability, easy repeatability, non-invasiveness, lack of radiation, and the option for use in combination with other intraoperative technologies; the main disadvantage is operator variability, because efficacy depends on skill and experience (Unsgaard 2006).

Fluorescence-guided surgery uses 5-aminolevulinic acid (5-ALA, or Gliolan (Medac, Wedel, Germany)) as a natural biochemical precursor of haemoglobin that elicits synthesis and accumulation of fluorescent porphyrins preferentially in mitotically active tissue (Regula 1995). Porphyrin fluorescence can be visualised with the use of a modified microscope and ultraviolet light with the aim of identifying neoplastic tissue (Stummer 1998; Stummer 2000). Limitations include lack of a clear boundary between neoplastic and eloquent tissue, and variability in uptake of 5-ALA depending on tumour characteristics. Distinct from iMRI and 3D US, both of which involve little cost after the initial outlay, is the cost per patient of each dose of 5-ALA, in addition to the requirement for a specific compatible operating microscope.

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, whilst for others the relationship is less clear (Hart 2011). Although high-quality evidence is lacking, estimated benefits of gross total resection include that it may extend survival from around 11 months to 14 months in glioblastoma, and from around 60 months to 90 months in low-grade glioma (Watts 2016). Limitations to the extent of surgical resection include ability to reliably identify residual tumour intraoperatively, availability of technology, and proximity of the tumour to eloquent tissue. Multiple technologies have been developed to aid intraoperative detection of residual tumour with the aim of extending resection. This information can be used by the surgeon to optimise resection, thereby potentially improving prognosis.

Why it is important to do this review

Experience with each different technology is often limited within individual units. Often, technologies are seen as an evolution of established techniques and are not subjected to the rigorous scrutiny required for other new therapies; therefore, evidence is often limited to small single-institution case series. Direct comparisons between different intraoperative imaging technologies are necessary to limit over-expenditure on redundant products.

Extending the extent of resection comes with the risk of encroaching upon eloquent brain areas. Potential benefits of more extensive tumour resection must be balanced against risks of new neurological deficits and reduced quality of life (QoL). This demands an objective assessment of risks and benefits for each technology.

This review aims to serve as a single comprehensive resource describing level of evidence and effectiveness for each technology.

OBJECTIVES

To establish the overall effectiveness and safety of intraoperative imaging in resection of glial tumours.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

This review will include people with presumed new or recurrent glial tumours (of any location or histology) from clinical examination and imaging (computed tomography (CT) and/or MRI). Additional imaging modalities (e.g. positron emission tomography, magnetic resonance spectroscopy) are not mandatory.

Types of interventions

Any of the following interventions can be compared with each other as well as within each intervention class (e.g. different forms of fluorescence-guided surgery).

- Intraoperative MRI (iMRI): defined as using a portable or fixed scanner (and moving scanner or patient, respectively) to acquire image data while the patient remains under anaesthesia. May be integrated with neuro-navigation (see below).
- Neuro-navigation or image guidance: defined as a system that integrates preoperative or intraoperative image data and creates a translation map between 'world space' and 'image space' to allow co-registration of imaging and patient anatomy, allowing neuro-navigation. Currently, the main trade systems are Brainlab (Codman Neuro, Raynham, Massachusetts, USA) and StealthStation (Medtronic Inc., Louisville, Colorado, USA).
- Intraoperative US (2D or 3D): defined as a system that uses freehand movement of a US probe over the region of interest and subsequently generates a volumetric reconstruction allowing intraoperative neuro-navigation. Currently, the main brand of intraoperative 3D US is Sonowand.
- Fluorescence-guided surgery: defined as administration of a contrast agent and intraoperative visualisation with the use of ultraviolet light (usually a specific mode of an operating microscope). Currently, the main agent used is 5-aminolevulinic acid (5-ALA), marketed under the trade name of Gliolan.

Types of outcome measures

Primary outcomes

- Extent of resection: as shown on follow-up imaging. Historically this has been broadly divided into complete resection (CR), partial resection (PR), and biopsy. Updated response criteria enable dichotomising this into measurable and non-measurable disease for contrast-enhancing lesions (Wen 2010). Volumetric assessment is a better method of assessment in terms of accuracy and objectivity but requires additional imaging processing time and is not used routinely in many NHS (National Health Service) centres. Intraoperative evaluation of extent of resection by the operating surgeon is a biased and unverifiable method and therefore is not acceptable (Hensen 2008). Percentage resection, residual, mean volumes, and percentage of total/non-total resection will be used

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

Secondary outcomes

- Overall survival: length of time (in days, weeks, or months) from randomisation to death (from any cause)
- Progression-free survival (PFS): use of open and thorough criteria to define recurrence according to clinical symptoms, imaging, and increase in steroid therapy (Wen 2010)

- Quality of life (QoL): use of a reliable and objective grading measure such as the EORTC QLQC30/BN-20 (European Organization for Research and Treatment of Cancer QoL assessment specific to brain neoplasms) and FACT-BrS (Functional Assessment of Cancer Therapy - brain subscale) (Mauer 2008)

We will present a 'Summary of findings table' to report the following outcomes, which are listed in order of priority (see Data synthesis).

- Extent of resection.
- Adverse events.
- Overall survival.
- Progression-free survival (PFS).
- QoL.

Search methods for identification of studies

Non-English language journals will be eligible for inclusion.

Electronic searches

We will search the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL; latest issue) in the Cochrane Library.
- MEDLINE (Ovid) (1946 to present).
- Embase (Ovid) (1980 to present).

We have presented RCT and Economic MEDLINE search strategies in Appendix 1 and Appendix 2, respectively.
For databases other than MEDLINE, we will adapt the search strategies accordingly.

Searching other resources

We will search the references of all identified studies for additional trials.

Handsearching

We will undertake a handsearch of *Journal of Neuro-Oncology and Neuro-oncology* from 1991 to 2017, to identify trials that may not have been included in the electronic databases, including a search of all conference abstracts published in these journals.

Personal communication

We will contact neuro-oncology experts to obtain information on current or pending RCTs.

Data collection and analysis

Selection of studies

We will identify studies in three stages. During title/abstract screening (for both intervention and economic analyses), we will use a machine learning classifier designed to distinguish RCTs from non-RCTs and will apply this tool to de-duplicated electronic search results (Wallace 2017). This classifier will assign a probability score to each retrieved citation (title-abstract record) that reports an RCT. Two review authors (MGH and DGB) will work independently to duplicate-screen citations with an assigned probability score greater than or equal to 0.1; we will automatically discard citations with a probability score less than 0.1.
Two review authors (MGH and DGB) will independently examine and screen remaining abstracts to see if they meet inclusion or exclusion criteria. Next, we will obtain full texts of selected reviews, which we will further examine and compare against the inclusion and exclusion criteria. At all times, we will resolve disagreements through discussion. If sufficient data are not available for assessment, we will contact relevant trial authors.

Data extraction and management

For included studies, two review authors (MGH and DGB) will independently abstract data using a prespecified form designed to gather information required for characteristics of included studies and validity tables (Juni 2001). We will resolve differences by discussion. Specific data extracted will include the following.

- Participant characteristics: age (mean and range), gender, performance status based on Karnofsky performance score (KPS) (Table 1) (Karnofsky 1948) or WHO score (Table 2) (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 identified will 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. Neuro-navigation: imaging sequences and timing, brand of equipment. 5-ALA: dose and timing, timing of ultraviolet light used intraoperatively, microscope used. Sonowand: brand, timing, operator experience. Additionally, surgical decision making influenced by intraoperative imaging should be stated.

- Outcome assessment: extent of resection (and measurement methods), overall survival, PFS, QoL, and adverse events. We will record additional quality control information on follow-up, as well as presence of an intention-to-treat (ITT) cohort, deviations from protocol, and post-recurrence management.

Assessment of risk of bias in included studies

We will critically appraise trials deemed relevant according to the criteria reported in NHS CRD Report No. 4 (CRD 2008). We will allocate trials according to risk of bias as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will cover specific core risk of bias items including selection, performance, detection, attrition, reporting, and other biases. Operator blinding is not possible, but participant and outcome assessment blinding will be desirable, although not mandatory. Two review authors (MGH and DGB) will provide independent critical appraisal. We will resolve disputes through discussion. See Table 3 and Table 4 for details of internal and external validity items (Fowkes 1991).

Measures of treatment effect

- Time-to-event data (survival and PFS): We will abstract the log hazard ratio (HR) and standard error (SE) of the log HR for imputing to RevMan 5 (Review Manager 2014). We will state the overall numbers of participants experiencing the event of interest during the trial period. If the HR and its variance are not presented (i.e. other survival data are presented, e.g. median survival, ranges or percentages at stated time points), we will attempt to abstract the data required to estimate these (Parmar 1998)

- Continuous outcomes (QoL and extent of resection): We will abstract the final value and standard deviation (SD) of the outcome of interest for each treatment arm at the end of follow-up.

- Dichotomous outcomes (adverse events, mortality, and extent of resection): We will abstract the number of participants in each treatment arm who experienced the outcome of interest to estimate a risk ratio (RR)

- Dichotomous and continuous data: We will abstract the number of participants assessed at each endpoint

When possible, all data abstracted will be those relevant to an ITT analysis. In the case of missing data required for review outcomes, we will contact study authors to request the information. Both review authors (MGH and DGB) will extract data and will enter them into RevMan 5.

Unit of analysis issues

We do not anticipate any unit of analysis issues.

Dealing with missing data

In the case of missing data required for review outcomes, we will contact study authors as needed. We will not impute missing outcome data.

Assessment of heterogeneity

We will assess heterogeneity between studies by visually inspecting forest plots, by estimating the percentage of heterogeneity between trials that could not be ascribed to sampling variation (Higgins 2011), and by performing a formal statistical test of the significance of identified heterogeneity (Deeks 2001).

Assessment of reporting biases

We intend to construct funnel plots of treatment effect versus precision to investigate the likelihood of publication bias. If these plots suggest that treatment effects may not be sampled from a symmetrical distribution, as assumed by the random-effects model, we will perform additional meta-analyses using the fixed-effect model.

Data synthesis

Review authors (MGH and DGB) will enter data into RevMan 5 and will pool data if trial characteristics (methods, participants, interventions, and outcomes) are similar.

- Time-to-event data: We will pool HR and variance using the generic inverse variance function of RevMan 5.

- Continuous outcomes: We will pool mean differences (MDs) between treatment arms at the end of follow-up using the MD method if all trials have measured the outcome on the same scale; we will use the standardised mean difference (SMD) method otherwise.

- Dichotomous outcomes: We will calculate the RR for each study and then will pool values for all studies.

We will use random-effects models for all meta-analyses (DerSimonian 1986) but may perform additional fixed-effect analyses if we find asymmetrical distribution (see Assessment of reporting biases).

We will present the overall quality of evidence for each outcome (see Types of outcome measures) according to the GRADE approach, which takes into account issues related not only to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity (e.g. directness of results) (Langendam 2013). We will create a 'Summary of findings' table (Appendix 2) based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and using GRADEpro GDT. We will use the GRADE checklist and GRADE Working Group quality of evidence definitions (Meader 2014). We will downgrade the evidence from 'high' quality by one level for serious concerns (or by two levels for very serious) for each limitation:

- High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

Owing to differences in prognosis, we will perform subgroup analyses according to tumour type, including:

- high-grade glioma (HGG);
- low-grade glioma (LGG); or
- primary versus recurrent disease in HGG and primary disease versus disease progression in LGG.

Sensitivity analysis

We will perform a sensitivity analysis to investigate how trial quality affects robustness of findings. We will perform a subsequent sensitivity analysis of trials that include objective blinded early postoperative MRI and histology in their assessment of extent of resection.

Brief economic commentary (BEC)

We will develop a brief economic commentary based on current methods guidelines (Shemlit 2011; Shemlit 2017) to summarise the availability and principal findings of trial-based and model-based economic evaluations (cost analyses, cost-effectiveness analyses, cost-utility analyses, and cost-benefit analyses) that compare the use of different intraoperative imaging technologies for patients with a presumed new or recurrent central nervous system (CNS) tumour. We will identify relevant studies for this brief economic commentary during searches conducted for the intervention review and during supplementary searches performed in accordance with search strategies developed by the Economic Method Group (Shemlit 2017). This commentary will focus on the extent to which principal findings of eligible economic evaluations indicate that an intervention might be judged favourably (or unfavourably) from an economic perspective, when implemented in different settings.

ACKNOWLEDGEMENTS

We would like to thank Gail Quinn, Clare Jess (Managing Editors), and Tracey Harrison (Assistant Managing Editor), for the CGNOC, for providing editorial support, as well as Jo Platt, Information Specialist, for devising the MEDLINE search strategy. We would also like to thank Ian Shemilt, EPPI-Centre, UCL, and Luke Vale, Institute of Health & Society, Newcastle University, for support provided in development of economic search strategies and associated methods.

This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure, to the Cochrane Gynaecological, Neuro-oncology, and Orphan Cancer Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, the NHS, or the Department of Health.

REFERENCES

Additional references

Black 1997
Black PM, Moriarty T, Alexander E 3rd, Stieg P, Woodard EJ, Gleason PL, et al. Development and implementation of intraoperative magnetic resonance imaging and its neurosurgical applications. *Neurosurgery* 1997;**41**(4): 831–42.

CRD 2008
Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in health care. York: York Publishing Services Limited, 2008. www.york.ac.uk/inst/crd.

Deeks 2001
Deeks JJ, Altman DG, Bradburn MJ. Systematic review in healthcare: meta-analysis in context. In: Egger M, Davey Smith G, Altman DG editor(s). *Statistical Methods for Examining Heterogeneity and Combining Results From Several Studies in Meta-analysis*. 2nd Edition. London: BMJ Publication Group, 2001.

DerSimonian 1986
DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**:177-88.

Fowkes 1991
Fowkes FGR, Fulton PM. Critical appraisal of published research: introductory guidelines. *BMJ* 1991;**302**:1136-40.

Hart 2011
Hart MG, Grant R, Metcalfe SE. Biopsy versus resection for high grade glioma. *Cochrane Database of Systematic Reviews* 2011, Issue 2. [DOI: 10.1002/14651858.CD002034]

Hensen 2008
Hensen JW, Ulmer S, Harris GJ. Brain tumor imaging in clinical trials. *American Journal of Neuroradiology* 2008;**24** (3):419–24.

Higgins 2011
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

Juni 2001
Juni P, Altman DG, Egger M. Assessing the quality of controlled clinical trials. *BMJ* 2001;**323**:42-6.

Karnofsky 1948
Karnofksy DA. The use of nitrogen mustards in the palliative treatment of carcinoma. *Cancer* 1948;**1**:634-56.

Langendam 2013
Langendam MW, Akl EA, Dahm P, Glasziou P, Guyatt G, Schunemann HJ. Assessing and presenting summaries of evidence in Cochrane Reviews. *Systematic Reviews* 2013;**23** (2):81.

Loius 2016
Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 WHO Classification of Tumours of the Central CNervous System: a summary. *Acta Neuropathologica* 2016;**131**:803–20.

Mauer 2008
Mauer ME, Bottomley A, Taphoorn MJB. Evaluating health-related quality of life and symptom burden in brain tumour patients: instruments for use in clinical trials and clinical practice. *Current Opinion in Neurology* 2008;**21**: 741-53.

Meader 2014
Meader N, King K, Llewellyn A, Norman G, Brown J, Rodgers M, et al. A checklist designed to aid consistency and reproducibility of GRADE assessments: development and pilot validation. *Systematic Reviews* 2104;**3**:82.

MedDRA 2008
Medical Dictionary for Regulatory Authorities (MedDRA). http:// www.meddramsso.com/MSSOWeb/index.htm, 2008.

NICE 2006
National Collaborating Centre for Cancer. Improving outcomes for people with brain and other CNS tumours - evidence review. http://www.nice.org.uk/nicemedia/live/ 10905/28965/28965.pdf.

Ohgaki 2009
Ohgaki H. Epidemiology of brain tumors. *Methods in Molecular Biology* 2009;**472**:323–42.

Parmar 1998
Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature of endpoints. *Statistics in Medicine* 1998;**17**:2815-34.

Regula 1995
Regula J, MacRobert AJ, Gorchein A, Buonaccorsi GA, Thorpe SM, Spencer GM, et al. Photosensitisation and photodynamic therapy of oesophageal, duodenal, and colorectal tumours using 5 aminolaevulinic acid induced protoporphyrin IX - a pilot study. *Gut* 1995;**36**:67-75.

Review Manager 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan) [Computer program]. Version 5.3.5 Copenhagen. The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Seifert 2003
Seifert V. Intraoperative MRI in neurosurgery: technical overkill or the future of brain surgery?. *Neurology India* 2003;**51**:329–32.

Shemlit 2011
Shemilt I, Mugford M, Vale L, Craig D, on behalf of the Campbell and Cochrane Economics Methods Group. Study report. Searching NHS EED and HEED to inform development of economic commentary for Cochrane intervention reviews. http://methods.cochrane.org/economics/workshops (accessed 13 July 2017).

Shemlit 2017
Shemilt I, Mugford M, Byford S, Drummond M, Eisenstein E, Knapp M, et al. on behalf of the Campbell and Cochrane Economics Methods Group. Chapter 15: Incorporating economics evidence In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Stummer 1998
Stummer W, Stocker S, Wagner S, Stepp H, Fritsch C, Goetz C, et al. Intraoperative detection of malignant gliomas by 5-aminolevulinic acid-induced porphyrin fluorescence. *Neurosurgery* 1998;**42**:518-25.

Stummer 2000
Stummer W, Novotny A, Stepp H, Goetz C, Bise K, Reulen HJ. Fluorescence-guided resection of glioblastoma multiforme by using 5-aminolevulinic acid-induced porphyrins: a prospective study in 52 consecutive patients. *Journal of Neurosurgery* 2000;**93**:1003-13.

Unsgaard 2006
Unsgaard G, Rygh OM, Selbekk T, Müller TB, Kolstad F, Lindseth F, et al. Intra-operative 3D ultrasound in neurosurgery. *Acta Neurochirurgica* 2006;**148**(3):235–53.

Wallace 2017
Wallace BC, Noel-Storr A, Marshall IJ, Cohen AM, Smalheiser NR, Thomas J. Identifying reports of randomized controlled trials (RCTs) via a hybrid machine learning and crowd sourcing approach. Journal of the American Medical Informatics Association [Internet]. 2017; Vol. 0, issue 0:1-4. https://academic.oup.com/jamia/article-lookup/doi/10.1093/jamia/ocx053.

Watts 2016
Watts C, Sanai N. Surgical approaches for the gliomas. *Handbook of Clincial Neurology* 2016;**134**:51–69.

Wen 2010
Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, et al. Updated response assessment criteria in high grade gliomas: response assessment in neuro-oncology working group. *Journal of Clinical Oncology* 2010; **28**(11):1963-72.

WHO 1982
Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology* 1982;**5**:649-55.

* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. 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

Table 1. Karnofsky performance score (*Continued*)

50	Requires considerable assistance and frequent medical care
40	Disabled: requires special care and assistance
30	Severely disabled: hospitalisation is indicated, death is not imminent
20	Very sick, hospitalisation is necessary: active treatment is necessary
10	Moribund, fatal processes are progressing rapidly
0	Dead

Table 2. 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 any 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 3. Internal validity

	Study 1	Study 2
Power calculation		
Randomisation methods		
Stratification at randomisation		
Allocation concealment		
Inclusion/exclusion criteria stated		
Group similarity at baseline		

Table 3. Internal validity (*Continued*)

Outcome assessment blinded		
Investigators blinded		
Participants blinded		
Objective outcome criteria		
ITT analysis		
Protocol deviations		
All participants accounted for		
Withdrawals specified		
Withdrawal reasons given		
Intercentre consistency		
Conflict of interest		

ITT: intention-to-treat

Table 4. External validity

	Study 1	Study 2
Age (mean and range)		
Sex (male:female)		
Performance score		
Histology		
Tumour locations		
Tumour enhancement		
Intervention		
Definitions		
Follow-up		

APPENDICES

Appendix 1. MEDLINE RCT search strategy

1. exp Central Nervous System Neoplasms/
2. ((central nervous system or CNS or brain* or cerebral* or intracerebral or intra-cerebral or intracranial or intra-cranial or spine or spinal or astrocytic or oligodendroglial or ependymal) adj5 (cancer* or tumor* or tumour* or malignan* or neoplas* or carcinoma* or metastat*)).mp.
3. exp neoplasms, neuroepithelial/
4. ((cranial or paraspinal or meninges or haematopoietic system or germ cell or germ-cell or sellar or glioneural or neuroectodermal or embryonal or neuroepithelial or pineal or choroid plexus or teratoid or rhabdoid) adj5 (tumor* or tumour*)).mp.
5. exp Glioma/
6. (glioma* or glial* 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* or GBM*).mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Magnetic Resonance Imaging/
9. (intra operative magnetic resonance imag* or intra-operative magnetic resonance imag* or intra operative MRI or intra-operative MRI or iMRI or ioMRI or IOMRI or IoMRI or MRI or MRi or NMRI or NMRi or magnetic resonance imag* or tractography).mp.
10. exp Ultrasonography/
11. ((2D or 3D) adj5 (ultras* or US)).mp.
12. ((intra-operative or intraoperative) adj5 (ultras* or US or IOUS or imag* or navigat* or technolog* or modalit* or eval* or monitor*)).mp.
13. (volumetric reconstruction or Sonowand or SonoWand).mp.
14. Neuronavigation/
15. Surgery, Computer-Assisted/
16. (navigat* or neuronavigat* or neuro-navigat* or image guid*).mp.
17. (Brainlab or Stealth).mp.
18. exp Monitoring, Intraoperative/
19. Fluorescence/
20. Aminolevulinic Acid/
21. (fluorescen* or immunofluorescen*).mp.
22. (aminolevulinic acid or 5-aminolevulinic acid).mp.
23. (ALA or 5-ALA or Gliolan).mp.
24. 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 or 22 or 23
25. 7 and 24
26. randomized controlled trial.pt.
27. controlled clinical trial.pt.
28. randomized.ab.
29. placebo.ab.
30. clinical trials as topic.sh.
31. randomly.ab.
32. trial.ti.
33. 26 or 27 or 28 or 29 or 30 or 31 or 32
34. (animals not (humans and animals)).sh.
35. 33 not 34
36. 25 and 35

Key

mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier

ab = abstract

sh = subject heading

ti = title
pt = publication type

Appendix 2. MEDLINE economic search strategy

1. exp Central Nervous System Neoplasms/
2. ((central nervous system or CNS or brain* or cerebral* or intracerebral or intra-cerebral or intracranial or intra-cranial or spine or spinal or astrocytic or oligodendroglial or ependymal) adj5 (cancer* or tumor* or tumour* or malignan* or neoplas* or carcinoma* or metastat*)).mp.
3. exp neoplasms, neuroepithelial/
4. ((cranial or paraspinal or meninges or haematopoietic system or germ cell or germ-cell or sellar or glioneural or neuroectodermal or embryonal or neuroepithelial or pineal or choroid plexus or teratoid or rhabdoid) adj5 (tumor* or tumour*)).mp.
5. exp Glioma/
6. (glioma* or glial* 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* or GBM*).mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Magnetic Resonance Imaging/
9. (intra operative magnetic resonance imag* or intra-operative magnetic resonance imag* or intra operative MRI or intra-operative MRI or iMRI or ioMRI or IOMRI or IoMRI or MRI or MRi or NMRI or NMRi or magnetic resonance imag* or tractography).mp.
10. exp Ultrasonography/
11. ((2D or 3D) adj5 (ultras* or US)).mp.
12. ((intra-operative or intraoperative) adj5 (ultras* or US or IOUS or imag* or navigat* or technolog* or modalit* or eval* or monitor*)).mp.
13. (volumetric reconstruction or Sonowand or SonoWand).mp.
14. Neuronavigation/
15. Surgery, Computer-Assisted/
16. (navigat* or neuronavigat* or neuro-navigat* or image guid*).mp.
17. (Brainlab or Stealth).mp.
18. exp Monitoring, Intraoperative/
19. Fluorescence/
20. Aminolevulinic Acid/
21. (fluorescen* or immunofluorescen*).mp.
22. (aminolevulinic acid or 5-aminolevulinic acid).mp.
23. (ALA or 5-ALA or Gliolan).mp.
24. 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 or 22 or 23
25. 7 and 24
26. economics/
27. exp "costs and cost analysis"/
28. economics, dental/
29. exp "economics, hospital"/
30. economics, medical/
31. economics, nursing/
32. economics, pharmaceutical/
33. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
34. (expenditure$ not energy).ti,ab.
35. (value adj1 money).ti,ab.
36. budget$.ti,ab.
37. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. ((energy or oxygen) adj cost).ti,ab.
39. (metabolic adj cost).ti,ab.
40. ((energy or oxygen) adj expenditure).ti,ab.

41. 38 or 39 or 40
42. 37 not 41
43. letter.pt.
44. editorial.pt.
45. historical article.pt.
46. 43 or 44 or 45
47. 42 not 46
48. Animals/
49. Humans/
50. 48 not (48 and 49)
51. 47 not 50
52. 25 and 51

Key

mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier
ab = abstract
sh = subject heading
ti = title
pt = publication type

Appendix 3. Draft 'Summary of findings' table

Example 'Summary of findings' table

Title:						
Patient or population: people with presumed new or recurrent glial tumours (of any location or histology) from clinical examination and imaging (CT and/or MRI) **Settings:** hospital setting **Intervention:** intraoperative imaging **Comparison:** surgery not using any image guidance or surgery using a different form of image guidance						
Outcomes	**Illustrative comparative risks***		**Relative effect (95% CI)**	No. of participants **(studies)**	**Quality of evidence (GRADE)**	**Comment**
	Assumed risk	**Corresponding risk**				
1 Extent of resection						
2 Adverse events						
3 Overal survival						
4 Progression-free survival (PFS)						

(*Continued*)

5 Quality of life (QoL)						

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. 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; HR: hazard ratio; MD: mean difference; OR: odds ratio; 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.

CONTRIBUTIONS OF AUTHORS

Damiano G Barone and Michael G Hart conceptualised the review and wrote the original protocol. Michael J Jenkinson and Colin Watts provided senior clinical commentary. Andrew Bryant and Theresa Lawrie provided expert methodological and statistical commentary.

DECLARATIONS OF INTEREST

Michael Jenkinson: no conflict of interest related to this protocol.

Andy Bryant: no conflict of interest related to this protocol.

Damiano Barone: no conflict of interest related to this protocol.

Michael Hart: no conflict of interest related to this protocol.

Colin Watts: no conflict of interest related to this protocol.

Theresa Lawrie: no conflict of interest related to this protocol.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.