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Intraoperative imaging technology to maximise extent of resection for glioma: a network meta-analysis (Protocol)

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[Intervention Protocol]

Intraoperative imaging technology to maximise extent of resection for glioma: a network meta-analysis

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ABSTRACT

Objectives

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

To establish the comparative effectiveness and risk profile of specific intraoperative imaging technologies using a network meta-analysis.

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BACKGROUND

Description of the condition

Of all primary tumours of the central nervous system, gliomas are the second most common representing 26.0%. The vast majority of gliomas are diffuse astrocytic and oligodendroglial tumours characterised by their diffusely infiltrative behaviour through the brain parenchyma (Louis 2016). This group includes IDH-mutant (isocitrate dehydrogenase) and wild-type genetic classifications across histological subtypes of diffuse astrocytoma, anaplastic astrocytoma, oligodendroglioma, anaplastic oligodendroglioma, and glioblastoma. Glioblastoma has a dismal prognosis; median survival in the UK is 6.1 months with a five-year survival of 3.4% (Brodbelt 2015). There is consensus for low-grade diffusely infiltrating gliomas and glioblastoma that maximising extent of resection is associated with a more favourable prognosis. Increasingly, intraoperative imaging technologies are being utilised in an effort to maximise the likelihood of gross total resection.

Description of the intervention

There are multiple modalities offering intraoperative imaging technology to assist the neurosurgeon in achieving maximal safe resection of gliomas. Fluorescence-guided surgery enables tumour tissue to be better visualised to maximise the probability of gross total resection of the enhancing component of gliomas. The most common fluorescent compound, 5-aminolevulinic acid (5-ALA), is a precursor of haemoglobin. Administered three hours before induction, the result is an accumulation of fluorescent porphyrins in mitotically active tissue. The fluorescence is visualised with ultraviolet light in order to identify neoplastic tissue intraoperatively in the surgical field and improve identification of resection margins (Stummer 1998; Stummer 2000). As a medication administration, there is an associated cost per single use. Capital investment required includes a fluorescence filter in any operating theatre microscope. The relative uptake of 5-ALA is dependent on the tumour characteristics, which limits its utility in accurately differentiating tumour and non-tumour tissue.

Imaging technologies currently variably used in the resection of glioma is intraoperative ultrasound (iUS), which relies on the different reflections of ultrasonic wave pulses caused by different tissue types enabling the delineation of neuroanatomical structures including normal-appearing cortex and brain tumour tissue. The ease in which images can be acquired using a hand-held device enables continuous assessment by the surgeon as resection proceeds.

Furthermore, this relatively affordable technique can be combined with a third technology, neuronavigation, in order to assist the neurosurgeon in achieving gross total resection. Neuronavigation leverages optical or electromagnetic technology to allow the registration of preoperative imaging on the patient in theatre. Several points are matched between the preoperative scan and the patient in theatre prior to computational registration of the scan on the patient in theatre. Specialised equipment visible to the neuronavigation software can then be used to plan the incision and craniotomy, and the trajectory of targeted biopsies.

The combination of iUS and navigation can overcome one major limitation of neuronavigation, namely brain shift. This occurs when the cranial cavity is entered resulting in a shift of intracranial contents relative to the preoperative scan due to the change in intracranial pressure and removal of cerebrospinal fluid (CSF) and tumour tissue. Such a shift can be adjusted for using iUS with simultaneous registration of three-dimensional (3D) iUS imaging on preoperative imaging. The software registers the position of the ultrasound probe and maps the 3D neuroanatomical image to allow adjustment of the preoperative imaging reflective of the brain shift that has occurred during the operation.

Finally, intraoperative magnetic resonance imaging (iMRI) involves the availability of either a nearby or portable magnetic resonance imaging (MRI) scanner for use in the operating theatre. MRI as an imaging technique involves creating a strong magnetic field, applying radiofrequency pulses, and analysing effects of this on the tissue of interest. Equivalent strength magnets are available to traditional MRI scanners offering clinically useful resolution to enable real-time intraoperative snapshot of the extent of tumour resection. Such a technique theoretically affords the possibility of immediate further resection during the same operative session (Black 1997). Unexpectedly, due to the need for a dedicated MRI scanner in the operating room, iMRI is associated with substantial capital costs both in terms of purchasing the scanner and its installation.

How the intervention might work

The purpose of all the above interventions are to maximise safe resection of the tumour, which, in the case of low-grade glioma (LGG) and high-grade glioma (HGG), have been associated with improved overall survival based on low-quality evidence (Hart 2019; Jiang 2017). The extent of resection is one of the only modifiable factors demonstrably correlated with overall survival and therefore is an important subject of research. A further benefit of improved detection of tumour and non-tumour tissue is the minimisation of damage to healthy brain tissue during the operation. In combination, these interventions can be used to maximise resection and improve prognosis and quality of life for the patients.

Why it is important to do this review

The technologies described are not used in all cases in all centres, and, prior to their introduction, were not subject to the same degree of scrutiny as new medical treatments including phase III studies. The capital costs associated with iMRI are substantial; an ability to compare a single or combination of technologies with alternatives is important to evaluate efficacy and cost effectiveness. Given the close relationship between achieving a greater extent of resection and the risk of surgical injury to healthy brain tissue, the associated risks of each technology and its effect on measures of quality of life will also be evaluated.

A review published in 2018 identified four randomised controlled trials (RCTS) of low-certainty evidence without network meta-analysis (Jenkinson 2018). Our review will appraise new evidence published since the publication of Jenkinson 2018, with additional quantitative analysis to facilitate direct and indirect comparisons of intraoperative imaging technologies used in isolation or in combination.

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OBJECTIVES

To establish the comparative effectiveness and risk profile of specific intraoperative imaging technologies using a network meta-analysis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs).

Types of participants

Participants included in RCTs with presumed new or recurrent glial tumours of any location of histology as identified based on clinical examination and neuroimaging (computed tomography (CT) or MRI, or both). Participant must also be eligible for randomisation to any intraoperative imaging modality.

Types of interventions

Through network meta-analysis, we will compare the following interventions with each other or against a standard of care of conventional microsurgery with white light.

- Fluorescence-guided surgery: defined as the use of a compound to facilitate the intraoperative delineation of tumour and normal brain tissue to assist the surgeon in performing maximal resection of the tumour.
- iUS (2D or three dimensional (3D)): defined as the use of an ultrasound probe for the identification of neuroanatomical structures including residual tumour tissue for evaluation of extent of resection.
- Neuronavigation/image guidance: defined as using preoperative imaging to identify intracranial neuroanatomy using optical or electromagnetic technology. Can be integrated with iMRI or iUS (or both) to update imaging to account for brain shift and tumour tissue removed during the treatment.
- iMRI: defined as a portable or fixed scanner with the acquisition of MRI to evaluate extent of resection while the patient remains under anaesthesia.

The interventions above are genuinely competing alternatives and in theory an RCT comparing all of the imaging techniques would be possible and participants could be randomly allocated to any of the interventions in isolation or combination. Moreover, combinations of interventions are also possible, particularly the concomitant use of iUS and image guidance to reduce problems associated with brain shift correction of preoperative imaging for brain shift.

Potential effect modifiers include the following.

- Fluorescence-guided surgery: exact compound used, time of administration, dose given, microscopic technologies used to detect fluorescence.
- iUS: 2D or 3D projections.
- Neuronavigation/image guidance: manufacturer software, optical or electromagnetic technologies.
- iMRI: use of portable or fixed scanner, sequences used, use of intravenous contrast agents.

Furthermore, as this review will include both newly diagnosed and recurrent glial tumours in any location, if differences in these variables are identified between included studies this could impact transitivity assumptions. The degree to which studies can be merged on the network will depend on the participants included and the interventions used, with splitting of the network to optimise transitivity when required.

Types of outcome measures

Primary outcomes

- Extent of resection: defined as the proportion of tumour tissue removed based on postoperative MRI imaging. Results presented as an absolute volume of resection, percentage resection, and categorical results (gross total resection, subtotal resection, biopsy) will be included.
- Adverse events: defined as need for unplanned additional procedures or development of complications including wound haematoma or infection, CSF leak, cerebral oedema, new or worsening focal neurological deficits or seizures, and general medical complications including thromboembolic disease or non-surgical site infection.

Secondary outcomes

- Overall survival: defined as length of time from randomisation to death.
- Progression-free survival: defined as length of time from randomisation in RCT to tumour progression based on RANO (Response Assessment in Neuro-Oncology criteria) consensus of imaging features of the contrast-enhancing and T2-weighted-fluid-attenuated inversion recovery (T2/FLAIR) non-enhancing component, new lesions, clinical deterioration not attributable to another cause, death, or other clear progression of unmeasurable disease (Wen 2010).
- Quality of life: defined based on validated measures for people with glioma including but not limited to the EORTC QLQ-C30 and BN20 (European Organization for Research and Treatment of Cancer Quality of Life assessment specific to brain neoplasms) questionnaires, and FACT-BrS (Functional Assessment of Cancer Therapy – Brain subscale) (Dirven 2014; Fountain 2016).

Our 'Summary of findings' table will report the following.

- Extent of resection.
- Adverse events.
- Overall survival.
- Progression-free survival.
- Quality of life.

We will make decisions on the certainty of the evidence for each outcome following the most recent recommendations and guidelines (Brignardello-Petersen 2018; Brignardello-Petersen 2019a; Brignardello-Petersen 2019b; Puhan 2014).

Search methods for identification of studies

Non-English language journals will be eligible for inclusion.

Electronic searches

We will search the following databases:

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

We have presented a MEDLINE search strategy in Appendix 1. For databases other than MEDLINE, we will adapt the search strategies accordingly.

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

Searching other resources

We will undertake a handsearch of the *Journal of Neuro-Oncology* and *Neuro-oncology* from 1990 to 2019 to identify trials that may not have been included in the electronic databases. This search will include all conference abstracts published in these journals.

Personal communications

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

Data collection and analysis

Selection of studies

Following automated deduplication of results, two review authors (DMF and DGB) will independently screen titles and abstracts, and assess them based on inclusion and exclusion criteria. We will import references to the bibliographical software database Endnote (latest available version). We will undertake full-text screening of all eligible studies at this stage and undergo further examination against inclusion and exclusion criteria. We will identify disagreements and resolve them through discussion.

Where studies have multiple publications, we will collate the reports of the same study so that each study, rather than each report, is the unit of interest for the review, and such studies have a single identifier with multiple references.

Data extraction and management

Two review authors (DMF and DGB) will independently extract data into a preprepared database designed based on an initial pilot of three studies. If sufficient data are not available from the published paper or additional supplementary material, we will contact authors to request relevant data for completion of the database for each study. We will identify differences in the extracted data between review authors and resolve them through discussion. The database will include the following fields.

- Participant characteristics: age, sex, performance status based on Karnofsky performance score (KPS) or World Health Organization (WHO) score, tumour location, contrast enhancement, tumour histology, tumour mutation status, and methylation status.
- Trial characteristics: inclusion and exclusion criteria, randomisation methods and stratification, allocation concealment (if applicable), blinding (of who and when), and statistics. Definitions identified will include extent of resection, progression, and adverse events.
- Interventions: iMRI field strength, imaging sequences, use of contrast, and reporting methods. iUS brand and operator experience, neuronavigation imaging sequences and brand, 5-ALA dose and timing of administration, use with a microscope.
- Outcomes: methods to calculate and measured extent of resection, overall survival, progression-free survival, and quality of life.
- Risk of bias in each study.
- Duration of follow-up.

We will produce 'Characteristics of included studies' and 'Characteristics of excluded studies' tables.

Data on outcomes will be extracted as follows.

- For dichotomous outcomes (e.g. extent of resection), we will extract the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at endpoint, in order to estimate a risk ratio (RR) and 95% confidence intervals (CI).
- For continuous outcomes (e.g. quality of life measures), we will extract the final value and standard deviation of the outcome of interest and the number of participants assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference between treatment arms and its standard error.
- For time to event data (survival and progression-free survival), we will extract the log of the hazard ratio (log(HR)) and its standard error from trial reports. If these are not reported, we will attempt to estimate the log (HR) and its standard error using the methods of Parmar 1998.

Where possible, all data will be extracted relevant to an intention-to-treat analysis in which participants are analysed in the groups to which they are assigned.

The time points at which outcomes were collected and reported will be noted.

Assessment of risk of bias in included studies

Two review authors (DMF and DGB) will provide independent critical appraisal, with any differences identified and resolved through discussion. We will assess risk of bias in all included RCTs in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). Types of bias considered will include selection, performance, detection, attrition and reporting bias. Additional bias in relation to potential conflicts of interest (industry funding / sponsorship) will also be considered. The influence of recorded risk of bias on the transitivity of data will be assessed.

Measures of treatment effect

We will measure the level of incoherence where possible (Chapter 11; Higgins 2019), with incoherence factors calculated and statistically tested. We will determine treatment effect measurements based on the type of data collected:

- continuous data: extent of resection, quality of life;
- time-to-event data: overall survival, progression-free survival;
- dichotomous data: extent of resection.

Unit of analysis issues

We do not anticipate any unit of analysis issues. We will conduct all network meta-analyses using Stata, which can deal with issues such

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as the inclusion of any multi-arm trials (i.e. adjust for the correlation between the effect sizes in the network meta-analysis) (Chaimani 2017).

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

In the first instance, we will decide whether or not included trials are sufficiently clinically and methodologically similar to perform a pair-wise analysis. If so, we will assess the transitivity assumption based on inclusion criteria (Salanti 2014), and, if not deemed sufficiently similar, we will not consider a network meta-analysis. Assuming trials appear similar enough to include, we will assess transitivity before we initially assess heterogeneity between studies by visually inspecting forest plots. We will base heterogeneity on participant characteristics, trial characteristics, and interventions to judge directness. For any pair-wise analyses in the review, we will report the I^2 statistic and interpret it according to guidelines reported in Section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

We will calculate the individual Q statistic for heterogeneity as part of obtaining direct treatment effects in the network meta-analysis. We will then calculate a Q statistic for inconsistency for global assessment across the network meta-analysis based on network estimates for direct and indirect comparisons (Efthimiou 2016). We will report the standard deviation (tau) of the between-studies heterogeneity as outlined in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

Assessment of reporting biases

For the meta-analysis or network meta-analysis (or both), we will 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

We will generate network plots to demonstrate which direct comparisons the included RCTs had made, with separate network plots for each prespecified outcome as available in the collected data.

If sufficient, clinically similar trials are available and we are satisfied the transitivity assumption is reasonable (see above), we will pool their results in network meta-analyses for each outcome. If a network meta-analysis is potentially dubious, we will attempt to report a conventional pair-wise meta-analysis if clinically and methodologically plausible.

- For any dichotomous outcomes, we will calculate the RR for each study and then pool these.
- For continuous outcomes, we will pool the mean differences between the treatment arms at the end of follow-up if all trials measured the outcome on the same scale, otherwise we will pool standardised mean differences.
- For time-to-event data, we will pool HRs using the generic inverse variance facility of Review Manager 5 (Review Manager 2014).

All network meta-analyses will be carried out in a frequentist framework using Stata using random-effects models with inverse variance weighting (Stata). We will make appropriate decisions about any variability in the interventions and will justify all comparisons and, if necessary, split the same interventions in the network if sufficiently different (e.g. measured in a different way).

From each of the network meta-analyses, we will additionally report the Surface Under the Cumulative Ranking curve Area (SUCRA) and mean rank statistics to accompany the effect estimates to aid in the interpretation of selecting the most effective imaging technique (Rücker 2015; Salanti 2011). We will examine trade-offs between the different outcomes and interpret all findings in light of risk of bias and GRADE profile for each outcome (GRADE Working Group 2004).

Subgroup analysis and investigation of heterogeneity

Owing to differences in prognosis, we will perform subgroup analyses or network meta-regression (if sufficient data are available) according to tumour type, including:

- HGG;
- LGG;
- 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.

Summary of findings and assessment of the certainty of the evidence

We will use the GRADE approach to assess confidence in estimates of effect (certainty of evidence) associated with specific comparisons, including estimates from direct, indirect, and final network meta-analysis (Brignardello-Petersen 2018; Puhan 2014; Salanti 2014). Our confidence assessment will address risk of bias (limitations in study design and execution); inconsistency (heterogeneity of estimates of effects across trials); indirectness (differences in population, interventions, or outcomes to the target of the network meta-analysis); and imprecision (e.g. 95% CIs are wide and include or are close to null effect). Limitations in any of these domains will result in a decrease of the certainty of evidence from high to moderate, low, or very low certainty by –1 (serious concern) or –2 (very serious concern). We will base indirect evidence on the most dominant loops (i.e. the shortest path between two treatments) and potentially rate it down for intransitivity (differences in study characteristics that may modify treatment effect in the direct comparisons along the path). We will obtain the final network meta-analysis confidence rating from the higher of the direct and indirect rating excluding imprecision and we will rate it down for imprecision and incoherence (difference between direct and indirect estimates). We will justify all decisions using footnotes

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and we will make comments to aid reader's understanding of the review where necessary.

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APPENDICES

Appendix 1. MEDLINE 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

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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

WHAT'S NEW

Date	Event	Description
26 May 2020	Amended	Affiliation update.

HISTORY

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CONTRIBUTIONS OF AUTHORS

DMF, AB and DB drafted the protocol.

All authors approved the final version of the protocol.

DECLARATIONS OF INTEREST

Daniel M Fountain: none known
Michael D Jenkinson: none known
Andrew Bryant none known
Luke Vale; LV was a member of NIHR HTA CET Panel until March 2018, He is the Co-ordinating Editor of Cochrane Incontinence which receives funding from NIHR and the host institution (Newcastle University) has received funding as part of a peer reviewed grant award by NIHR to conduct the specified work.
Helen Bulbeck: none known
Michael G Hart: none known
Damiano Giuseppe Barone: none known

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