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Utility of 5-ALA for resection of CNS tumours other than high-grade gliomas: a protocol for a systematic review

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ABSTRACT

Introduction 5-aminolevulinic acid (5-ALA) is a proagent developed for fluorescent-guided surgery for high-grade glioma patients associated with a significant increase in resection conferring survival. 5-ALA was shown to penetrate the blood–brain barrier accumulating in malignant glioma cells with high selectivity, sensitivity and positive predictive value. However, those have yet to be explored aiding diagnosis for tumours of the central nervous system (CNS) other than high-grade gliomas (HGG). No up-to-date systematic review exists reporting the major surgical outcomes and diagnostic accuracy. We sought to conduct a systematic review of the literature summarising surgical outcomes, evaluate the quality of diagnostic accuracy reported in the literature and qualitatively assess the evidence to inform future studies.

Methods and analysis We will search electronic databases (Medline, Embase) with subsequent interrogation of references lists of articles reporting the use of 5-ALA for brain tumours other than high-grade glioma adult patients, which also report the extent of resection and/or survival. Prospective and retrospective cohort and case–control studies with more than five patients will be included. Two independent reviewers will screen the abstracts and full articles, with a third reviewer resolving any conflicts. The data will be extracted in a standardised template and outcomes will be reported using descriptive statists. The quality of non-randomised studies will be appraised.

Ethics and dissemination The study will summarise the available evidence on the effect of the clinical utility of 5-ALA in achieving resection and improving survival and its diagnostic accuracy for tumours of the CNS other than HGG. The data will be presented nationally and internationally and the manuscript will be published in a peer-reviewed journal. No ethical approvals were needed. The aim is to inform prospective studies minimising reporting bias allowing for more reliable, reproducible and generalisable results. The study has been registered in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

PROSPERO registration number
CRD42021260542.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Protocol to formally and systematically review the literature for an emerging indication for 5-Aminolevulinic acid (5-ALA) that has not been reviewed before.
⇒ A comprehensive summary of the existing evidence to examine the impact of 5-ALA on resection and to evaluate whether the subsequent impact on survival is reported.
⇒ A comprehensive summary of the existing evidence to qualitatively assess the studies conducted to date and raise the standards for similar undergoing studies especially with regard to diagnostic accuracy.
⇒ To our knowledge, no randomised controlled trial was published on this subject though at least one is undergoing, therefore, our systematic review will meta analyse evidence that is not level I, thus, no definite evidence will be generated from this review.

INTRODUCTION

5-aminolevulinic acid (5-ALA) is an agent for fluorescence-guided surgery (FGS), which is currently approved by the US Food and Drug Association and recommended by the National Institute for Health and Care Excellence and the European Association of Neuro-Oncology as a surgical adjunct in aiding maximal-safe resection of high-grade gliomas (HGG).[1–3] 5-ALA was shown to penetrate the blood–brain barrier, accumulating within malignant gliomas, demonstrating high sensitivity, specificity and positive predictive value (PPV) in numerous studies.[4–7] It is preferentially taken up by malignant glioma cells to be intercellularly converted to the fluorescent metabolite, protoporphyrin IX (PpIX).[8] The high uptake of 5-ALA within malignant tumour cells leads to a violet-red fluorescence visualisation of tumour tissue after excitation with blue light, enabling real-time intraoperative visibility of the tumour and subsequent resection.[9] Factors influencing the visible violet-red fluorescence under a microscope

includes the density of malignant cells, proliferative activity and neovascularity of the tumour.[7 10]

HGGs are the most aggressive primary brain tumours known, with poor progression-free (PFS) and overall survival (OS).[11] The current neurosurgical standard of care promotes maximal-safe resection of contrast-enhancing tumours whenever possible. While complete or near-complete safe resection is very challenging due to the risk of neurological morbidity and achieved in 36% of the cases, there is sufficient evidence to suggest it is associated with increased OS and PFS.[12 13] The intraoperative difficulty in distinguishing viable tumours from normal adjacent brain tissue led to the development of FGS with a surge in publications over the past decade.[14] A randomised, controlled phase III trial confirmed a significant increase in resection of malignant gliomas and PFS when 5-ALA was used compared with white-light microscopy with subsequent observational studies demonstrating increased resection rates globally.[15–17] 5-ALA is now a standard of care in a plethora of countries for HGG deemed feasible for complete resection.

The pathological features of malignant gliomas that is, increased proliferation, angiogenesis is not only shown by HGG. Diffusely infiltrative gliomas showing no significant enhancement in T1-weighted MRI with contrast are presumed to be low-grade gliomas (LGG). However, close to 50% of radiologically suspected LGGs contain anaplastic and/or malignant foci.[18] It is now recognised that the majority of LGG will eventually transform to HGG with a devastating prognosis.[19] Therefore, the intraoperative identification and removal of malignant/anaplastic foci are paramount in any surgical strategy to limit progression. Moreover, the postoperative treatment of HGG differs significantly from LGG with implications for long-term morbidity and quality of life. Identification of foci of malignant transformation within LGG could transform postoperative care. Recent studies have demonstrated that 5-ALA can facilitate the visualisation of such anaplastic foci in many patients[20–22] and improve resection rates.[23] This means that the potential removal of 5-ALA fluorescence foci within an LGG tumour may have an impact on resection and subsequent patient survival.

Despite the effort to delineate why 5-ALA might be preferentially taken up by glioma malignant cells, no clear biochemical explanation currently exists through a decreased expression of ferrochelatase, a mitochondrial enzyme converting PpIX to heme, might lead to the preferential PpIX accumulation.[24 25] It is postulated that 5-ALA may offer benefit for aiding the resection of other malignant tumours of the central nervous system (CNS), both primary and secondary (metastatic tumours to the CNS) and thus lead to improved survival outcomes.[26–29] Indeed, several observational studies emerged over the last decade reporting increased resection rates and visible intraoperative 5-ALA fluorescence for meningiomas, lymphomas and metastatic CNS tumours.[30–35] A meta-analysis on the usage of 5-ALA FGS using a narrow search strategy capturing meningiomas was conducted in 2016, only reporting intraoperative visible fluorescence and resection rates but no long-term postoperative outcomes including survival were reported.[36] Since then, a plethora of studies has emerged reporting new outcomes of using 5-ALA for a variety of tumours of the CNS other than HGG including meningiomas. According to our knowledge, no up-to-date systematic review of the literature exists collating and quantifying the level of evidence for the usage of 5-ALA for adult patients diagnosed with a tumour of the CNS other than an HGG, reporting visible fluorescence rates, resection and survival rates, and with an extensive search strategy.

Lastly, the notion of diagnostic accuracy falls within the remit of clinical utility. Stummer *et al* have systematically reviewed the quality of the literature regarding the ability of fluorescence imaging to highlight tissues that truly represent tumour.[37] It has been argued that higher-quality studies are needed to better characterise the sensitivity, specificity, PPV and negative predictive value (PPV, NPV). Prospective studies of diagnostic accuracy should reflect on the fact that high-grade tumours are infiltrative and can invade nearby tissues thus hinter the results of tumour versus 'normal' tissue sampling. Further, the number of tumour tissue biopsies from the same patient, the spatial distribution of tissue sampling within the tumour and the normal tissue biopsy distance from the tumour-normal tissue boundary, are likely to affect results. The additional bias of pooling a heterogeneous number of biopsies per patient in a large pool of biopsy samples to predict PPV and NPV is likely to impact the outcome. This encouraged them to develop a framework for an objective qualitative assessment of diagnostic accuracy applied to glioma tissue sampling, which has never been used for other tumours of the CNS. We aim to adopt these standards of reporting diagnostic accuracy to critically assess the literature regarding the use of 5-ALA for the diagnosis of CNS tumours other than HGG. We intend to raise the bar of quality for research to be able to report outcomes based on more rigorous and stringent methodologies, minimising potential cofounders and biases that may alter the results. Research recommendations will be made for the best interest of the public and patients.

We sought to conduct an up-to-date comprehensive systematic review of the literature and meta-analysis if specific tumour types are well represented and screening of heterogeneity allows. We aim to collate important operative and postoperative outcomes including visible intraoperative fluorescence, tissue sampling techniques, the extent of surgical resection and survival. This will allow researchers to select the most promising tumour types to conduct future studies including (1) randomised trials examining whether 5-ALA can add benefit to surgical resection and improve survival and (2) prospective diagnostic accuracy studies to accurately evaluate the ability of fluorescent tissue sampling to identify CNS tumours.

Table 1 Planned inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	Adult patients (>16 years) with a histopathological diagnosis of a tumour of the CNS other than HGG: (1) diffuse astrocytoma, (2) oligodendroglioma, (3) diffuse midline glioma, (4) meningioma (5) lymphoma (6) metastatic tumours to the CNS, (7) ependymoma (8) papillary tumour of the pineal (9) schwannoma.	Paediatric patients <16 years of age. A histopathological diagnosis of a high-grade glioma.
Intervention/ comparator	Usage of 5-ALA aiming for resection. Studies with alternative surgical adjuncts in combination with 5-ALA will be included but it is anticipated that there will few studies with a comparator group	No usage of 5-ALA.
Outcome	Primary: Extent of surgical resection either as a binary outcome of complete versus non-complete resection of enhancing tumour of continuous outcome of percentage of resection of contrast-enhancing tumour in T1-weighted MRI with contrast. Secondary: The progression free or overall survival reported in weeks/months or years. Adverse effects and deficits reported will be included. Systemic disease developed after use of 5-ALA and performance status of patients will be captured. Fluorescent patterns, specificity, sensitivity, positive and negative predictive value	Studies describing fluorescence patterns with incomplete data regarding the extent of surgical resection will be included. Studies not reporting resection or survival or fluorescent patterns will be excluded
Study design	Prospective and retrospective observational cohort and case–control studies with >5 patients.	Case reports, abstracts, editorials and radnomised studies (if any) will not be included. According to our knowledge, no randomised study exists.

5-ALA, 5-aminolevulinic acid; CNS, central nervous system; HGG, high-grade gliomas.

Objectives

1. Systematically review literature capturing, cohort, case–control, prospective and retrospective studies that evaluate the use of 5-ALA for CNS tumours other than HGG.
2. To determine: (1) intraoperative visible fluorescence, (2) resection and (3) survival (4) safety of the tumours above.
3. To evaluate the quality of reporting outcomes of diagnostic accuracy.

METHODS AND ANALYSIS

Protocol

The methodology of this systematic review and the protocol writing has been developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol guidelines. The study protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) on (CRD42021260542).

ELIGIBILITY CRITERIA

This will include prospective and retrospective cohort and case–control studies with a minimum of 5 subjects (table 1). Case reports will not be included. According, to our knowledge, no randomised study yet exists to evaluate 5-ALA for the use of brain tumours other than HGG. Adults (>16 years of age) with primary and secondary tumours of the CNS of histological type as follows: (1) diffuse astrocytoma, (2) oligodendroglioma, (3) diffuse midline glioma, (4) meningioma (5) lymphoma (6) metastatic tumours to the CNS, (7) ependymoma (8) papillary tumour of the pineal and (9) schwannoma. Studies with alternative surgical adjuncts in combination with 5-ALA will be included but it is anticipated that there will be few studies with a comparator group. Studies not reporting resection and/or fluorescence and/or survival for the patient cohort will not be included. Studies limited to evaluating paediatric patients will not be included since a review of the literature is already available. Studies including biopsy surgery only will be included.

Outcome measures

The following outcome measures will be included:

1. (A) Intraoperative visible fluorescence under blue light microscopy. (B) The pattern of fluorescence: heterogenous vs whole-tumour. (C) Sensitivity, specificity, positive and negative predicting value. (D) Resection: volumetric studies, complete resection of contrast-enhanced tumour.
2. (E) Postoperative neurological complications: infection, stroke, seizure, CSF leak, haematoma, death within 30 days. (F) Postoperative deficits: motor, sensory, language, vision, cognition. (G) survival: OS and PFS in days/weeks/months/years.

Search strategy

Medical subject headings (MeSH), Thesaurus and 'keywords' were used to develop a literature search

strategy to search the title, abstract, name of substance word and subject heading word (online supplemental appendix 1). The search strategy was developed in collaboration with an information specialist. We will search MEDLINE (OVID interface 2006–May 2021), EMBASE (OVID interface, 2006–May 2021). We will also interrogate the reference lists of those studies and reviews meeting our inclusion criteria.

Data collection

At least two independent, blinded reviewers (GS, AG, MG, AV, CSG and WP) will screen titles and abstracts for eligibility, and a third validator and senior author (PP) to resolve any issues will be consulted if any disagreements occur that cannot be resolved by consensus. Subsequently, two independent reviewers (AG, MG, AV, CSG and WP) will then screen the full text of the remaining articles for inclusion, with disagreements resolved by discussion and an independent third reviewer (GS). Studies will be entered to Rayyan a free online reference management software programme acting as a database to manage articles. An Excel sheet will be kept for reviewers to keep a record of decision making with an explanation based on the study inclusion/exclusion criteria. Following submission of the protocol for publication, the abstract screening, data extraction, data analysis and manuscript drafting will be conducted between 29 January 2022 and 30 March 2022. The search strategy included abstracts to be a screen between the 1 January 2006 and May 2021 (the date that this protocol was finalised).

Data items

Will include:

- Author, date of publication, country of origin, journal of publication, funding and conflict of interest, informed consent.
- Study characteristics—the type of study (prospective/retrospective, cohort, case–control).
- Participant's characteristics—gender, age, number of participants, neurological function
- Tumour characteristics—location, histological type, grade, molecular diagnosis, contrast enhancement.
- Intervention characteristics—5ALA, other intraoperative technology used including neuronavigation, intraoperative ultrasound, awake surgery, electrophysiological monitoring.
- Outcome characteristics—visible fluorescence, the patter of fluorescence, sensitivity, specificity, positive predicting value, negative predicting value, the extent of resection, postoperative complications and deficit, performance status, systemic disease developed, PFS and OS.

Risk of bias (quality) assessment

We will use the Risk Of Bias In Non-randomised Studies-of Interventions. This will assess (1) confounding, (2) selection of participants into the study, (3) classification of interventions, (4) deviation from intended interventions, (5) missing data, (6) measurement of outcomes and (7) selection of the reported result. For diagnostic accuracy recommendations by Stummer *et al* as well as the Standards for Reporting of Diagnostic Accuracy Studies will be used to evaluate bias including tissue allocation bias type A, B and C, bias from biopsy frequency, pooling samples from different patients, timing bias and bias from histological assessment.[37 38] Further, we will evaluate whether diagnostic accuracy studies have assessed all four terms: specificity, sensitivity, PPV, NPV.

Data synthesis and analysis

Data will be entered into a premade excel sheet, with relevant adjustments as required during the extraction process. Discrepancies in data extraction will be resolved among team members. The findings will be tabulated, and descriptive statistics will be performed. Data will be categorised into descriptive themes such as tumour types and primary outcomes of interest and if specific tumours types are well represented then a meta-analysis will be considered. A narrative synthesis will be performed summarising key outcomes by tumour type. Further, tables will be presented to show whether critical elements of bias have been considered as per Stummer *et al* paper[37] and whether specificity, sensitivity, PPV, NPV are been reported.

Dissemination, patient and public involvement

The systematic review will be published in a peer-reviewed journal and presented in national and international meetings. This protocol can be used and adapted for other FGS adjuncts. Patients and the public were not directly involved in the design, conduct or reporting of this protocol. However, we hope to include charity bodies to disseminate the results of the systematic review once is completed.

Taking into consideration that the literature is growing and numerous studies appear every year evaluating this topic, we should systematically summarise key data to optimise future studies to be conducted. We will highlight areas where reporting of outcomes should be improved. Further, our data will subsequently allow the best possible selection of tumour types, and patients to be selected evaluating the specificity, sensitivity, PPV and NPV of 5-ALA for the most promising tumour types. Finally, feasibility randomised studies can be conducted for improving patient outcomes.

The growing literature in this field suggests an exponential increase of studies in the future. We aim to provide a framework of reporting bias in an attempt to improve the quality of future research regarding diagnostic accuracy. We consider this as a pertinent question since answering objectively whether the fluorescent tumour represents viable malignant tissue only and not healthy tissue is paramount affecting its clinical utility and subsequent surgical outcomes. This is in the best interest of the patients as it is likely to minimise harm and augment the possible benefit.

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