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5-Aminolevulinic acid for recurrent malignant gliomas: A systematic review

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ABSTRACT

Objectives: Nowadays, several techniques have been developed in order to guide neurosurgeons during intended maximal safe resection of high-grade gliomas (HGG). Fluorescence-guided microsurgery using 5-aminolevulinic acid (5-ALA) is one of these. A large amount of studies have been performed evaluating benefits in newly diagnosed HGG. However, little is known about the safety, accuracy and efficacy in recurrent HGG.

The primary objective of this thesis is to examine the value of 5-ALA in patients with recurrent HGG concerning diagnostic accuracy, extent of resection (EOR), safety and survival compared to white-light resection. As a secondary objective, we compared these results with current literature concerning 5-ALA in newly diagnosed HGG.

Patients and methods: We performed a systematic review and included eighteen articles obtained from MEDLINE, EMBASE, Web of Science and TRIP database. Search terms include “glioma” and “aminolevulinic acid”. Additional studies were identified through checking the reference lists. This study is in conformity with the PRISMA and BMJ guidelines.

Results: 5-ALA shows similar results regarding diagnostic accuracy in recurrent HGG compared to newly diagnosed HGG, although specificity and negative predictive value seem lower. It shows complementary value in identifying tumor boundaries compared to MRI-neuronavigation. Diagnostic accuracy is not influenced by previous chemo- or radiotherapy. New neurological deficits proved to be similar and were in general mainly temporary. However, adverse events overall were more common. Therefore, indications for repeat surgery should be followed strictly. 5-ALA might increase overall survival in recurrent gliomas, but has no clear impact on progression-free survival.

Conclusion: 5-ALA should be regarded as a useful and safe intraoperative tool in recurrent glioma surgery.

Abbreviations: 18F-FET-PET, 18F-Fluoro-Ethyl-Tyrosine Positron-Emission-Tomography; 5-ALA, 5-Aminolevulinic Acid; A, Astrocytoma; AA, Anaplastic Astrocytoma; AC, Adenocarcinoma; AE, Adverse Events; AF, Atrial Fibrillation; AO, Anaplastic Oligodendroglioma; AOA, Anaplastic Oligoastrocytoma; AUC, Area Under the Curve; AVM, Arteriovenous Malformation; BBB, Blood-Brain-Barrier; BMJ, British Medical Journal; CA, Cavernous Angioma; CPOX, CoproPorphyrinogen-III Oxidase, Mitochondrial; E, Ependymoma; EOR, Extent Of Resection; FGS, Fluorescence-Guided Surgery; FN, False Negative; FP, False Positive; GBM, Glioblastoma Multiforme; Gd-DTPA, Gadolinium-DiethyleneTriamine Pentaacetic Acid; GTR, Gross-Total Resection; HGG, High-Grade Glioma; HS, Hippocampal Sclerosis; IDH1, Isocitrate DeHydrogenase 1; IDH2, Isocitrate DeHydrogenase 2; iMRI, Intraoperative Magnetic Resonance Imaging; KPS, Karnofsky Performance Scale; LGG, Low-Grade Glioma; LR, Likelihood Ratio; MeSH, Medical Subject Headings; MET, Metastases; MRI, Magnetic Resonance Imaging; NIHSS, National Institutes of Health Stroke Scale; NPV, Negative Predictive Value; NS, Non-Specific; O, Oligodendroglioma; OA, Oligoastrocytoma; OR, Odds Ratio; OS, Overall Survival; P, Primary; PE, Pulmonary Embolism; PFS, Progression-Free Survival; PICO, Patient-Intervention-Comparison-Outcome; PIRT, Patient-Index-test-Reference-test-Target-condition; PLGG, Progression from Low-Grade Glioma; PNND, Postoperative New Neurological Deficits; PPIX, Protoporphyrin IX; PPV, Positive Predictive Value; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QUORUM, Quality Of Reporting of Meta-analyses; R, Recurrent; RANO, Response Assessment in Neuro-Oncology; RCT, Randomised Controlled Trial; ROB, Risk Of Bias; ROBINS-I, Risk Of Bias In Non-randomised Studies of Interventions; SCC, Spinocellular Carcinoma; SF, Strong Fluorescence; STARD, Standards for Reporting Diagnostic Accuracy; STROCSS, Strengthening the Reporting Of Cohort Studies in Surgery; TRIP, Turning Research Into Practice; TTP, Time to Tumor Progression; WF, Weak Fluorescence; WHO, World Health Organization; WLR, White-Light Resection

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- What is already known on this subject

Since the first publication on the usage of 5-aminolevulinic acid (5-ALA) in the treatment of glioblastoma multiforme by the ALA-Glioma Study Group, many reviews have been published on this subject. It is already known that the extent of tumor resection is correlated with an increase in survival. Intraoperative 5-ALA fluorescence has a very favourable diagnostic accuracy during the treatment of newly diagnosed high-grade gliomas (HGG).

- What this systematic review adds

Although studies evaluating the application of 5-ALA in the treatment of recurrent HGG have been performed in current literature, most of these studies are characterised by a small study size. Therefore, this article forms a comprehensive systematic review analysing benefits of 5-ALA in recurrent HGG concerning diagnostic accuracy, extent of resection, safety and survival.

1. Introduction

High-grade gliomas (HGG) constitute the most common newly diagnosed malignant brain tumor in adults. Of these, glioblastoma multiforme (GBM) is the most prevalent [1–3]. Invasiveness is a hallmark of these tumors, impeding the intraoperative distinction between normal and pathological tissue [4–7]. As a consequence, recurrence is a major concern [8]. Nevertheless, extent of resection (EOR) is correlated with a gain in progression-free survival (PFS) [9–18], mainly in newly diagnosed HGG [10,14,15,19–21]. Therefore, according to the Stupp protocol, microsurgical resection followed by concomitant chemoradiotherapy forms the gold standard [1,22,23].

Nowadays, several techniques have been developed in order to guide neurosurgeons during maximal safe resection. One of these techniques is fluorescence-guided surgery (FGS) using 5-aminolevulinic acid (5-ALA) (Fig. 1). The first publication by the ALA-Glioma Study Group in 2006 in patients with GBM was a breakthrough in FGS research [24]. A significantly higher incidence of gross total resection (GTR) was achieved compared to conventional white-light resection (WLR).

5-ALA is a relatively recent tool in the brain surgery repertoire [4,25–27]. Until now, it is the only fluorescent tumor-cell specific agent that has been tested in a multicenter randomised controlled trial [28]. 5-ALA is the first metabolite in the heme-biosynthesis-pathway, both in normal and pathological tissues [29]. After mitochondrial uptake, it is metabolized into protoporphyrin IX (PPIX) [27,30]. In contrast to the non-fluorescent amino acid 5-ALA, PPIX owns a strong fluorescent capacity [26]. Furthermore, 5-ALA seems to have a radio-sensitizing effect [31]. The last step in the heme-biosynthesis-pathway is the incorporation of iron into PPIX, regulated by the enzyme ferrochelatase. PPIX accumulation can be visualized as red fluorescence using a modified microscope with blue-violet illumination [25–27,32].

Despite multiple hypotheses, it is still not completely clarified why PPIX is preferentially accumulated in HGG. CPOX upregulation [33], ferrochelatase downregulation [33,34], increased cell density [35] and distortion of normal blood-brain-barrier (BBB) are the most common encountered theories in current literature [36–39]. The latter seems reasonable, since the hydrophilic molecule cannot cross the intact BBB [26]. This underlines the need for a damaged BBB for PPIX to accumulate within tumor cells. It has been proven that 5-ALA accumulates in other tissues as well, such as low-grade gliomas (LGG), choroid plexus, ependymomas, meningiomas and intracerebral metastases (MET) [40–44]. It also seems to occur in anaplastic foci, making these lesions visible intraoperatively [45–47]. In contrast, normal brain tissue shows a very limited amount of accumulation. Accumulation is more pronounced in the solid tumor part, but is also present in the infiltration zone. Removal of the solid part has the greatest influence on survival rate [48–50].

The absence of fluorescence does not always indicate the absence of malignant cells [51]. One explanation is photo-bleaching, in which fluorescence deteriorates under the influence of light [32]. This phenomenon probably only plays a minor role. Another cause is delayed 5-ALA administration prior to surgery [5]. However, a sufficient amount of fluorescence was observed even twelve hours after oral application [5,32]. On the other hand, positive fluorescence not always proves the existence of HGG, since fluorescence has been observed in benign lesions as well, such as abscesses or vasculitis [52–56]. Even in the absence of PPIX, many tissues show some fluorescence caused by autofluorescence [54]. Rarely, it can even been detected in normal brain tissue [57–62]. Nevertheless, intensity of intraoperative fluorescence correlates well with tumor cellularity, both in newly diagnosed and recurrent HGG, making it an ideal predictor for malignancy [15,62,63].

5-ALA is administered orally three to four hours prior to anesthesia. Target cells are almost immediately reached, with maximal concentrations after six hours. Within three to four hours, the substance has been excreted. A maximum dose of 20 mg/kg is most commonly used [30,32]. Higher doses are associated with an increase in adverse events (AE) [64]. Hypotension, liver dysfunction and skin photosensitivity are occasionally encountered [4,21,61,62,65,66]. Metabolic AE (e.g. increased liver enzymes) and changes in biochemical parameters (e.g. renal dysfunction) resolve spontaneously within the first twenty-four hours [67]. Since 5-ALA is a diagnostic – rather than a therapeutic – tool, much attention should be paid to safety and compound-related AE. However, since it has little intrinsic activity on normal brain tissue, neurological AE should be attributed to surgery, rather than the compound itself.

Although repeated surgery may be beneficial in recurrent HGG, there are some important hazards. Due to gliosis in the previously manipulated brain, anatomical landmarks are affected, making the boundary between normal and abnormal brain tissue even more distorted. Furthermore, there is an increased risk of causing neurological deterioration caused by over-resection. Therefore, 5-ALA should be used with caution. Main clinical observations in the usage of 5-ALA in the treatment of recurrent HGG are depicted in Fig. 3.

Since the approval of 5-ALA in HGG resection by the European Medicines Agency and recently by the Food and Drug Administration, a large amount of studies have been performed evaluating benefits in

Fig. 1. Intraoperative 5-ALA fluorescence during (A) and after (B) resection of a high-grade glioma.

newly diagnosed HGG. However, little is known about long-term survival and postoperative results in recurrent HGG. Therefore, the primary objective of our review is to analyse benefits of 5-ALA in recurrent HGG concerning diagnostic accuracy, EOR, safety and survival compared to conventional WLR. As a secondary objective, we compared our results with current literature regarding 5-ALA usage in newly diagnosed HGG. Therefore, this article forms a comprehensive systematic review analysing benefits of 5-ALA in recurrent HGG concerning diagnostic accuracy, extent of resection, safety and survival.

2. Methods and materials

2.1. Research protocol

We performed a systematic review in which intraoperative 5-ALA usage was compared with conventional WLR in patients with recurrent HGG. This review was conform the 27-item checklist of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the British Medical Journal guidelines [68,69].

The primary objective was to analyse benefits of 5-ALA in patients with recurrent HGG concerning diagnostic accuracy, EOR, safety and survival compared to WLR. As a secondary objective, we compared our results with current literature concerning 5-ALA usage in newly diagnosed HGG and looked for notable differences.

2.2. Search strategy, eligibility criteria, data extraction and quality assessment

2.2.1. Search strategy

An adequate research question was formulated (Appendix A). The used model was depending on the examined objective. We used the Patient-Intervention-Comparison-Outcome model for the objectives "survival" and "safety", while "diagnostic accuracy" and "extent of resection" were investigated using the Patient-Index-test-Reference-test-Target-condition model (Table 1). According to these models, we derived corresponding Medical Subject Headings (MeSH-terms). Due to the limited available literature regarding 5-ALA usage in recurrent HGG, we used a minimal amount of MeSH-terms, reducing the risk of overlooking relevant literature. The following methodological filters were used to exclude irrelevant literature: "full text only" and "human studies". First and last searches were performed on 31st of March and 1st of November 2018, respectively. SB was responsible for database searches, abstract screening and quality assessment. Final inclusion was done after discussion with and approval by the senior author.

2.2.2. Information sources

We used the MEDLINE (PubMed), EMBASE, Web of Science and Turning Research Into Practice databases. Reference lists were also checked for additional studies. Ongoing clinical trials were checked using the International Standard Randomised Controlled Trial Number registry and PROSPERO. Grey literature (research published in non-commercial form) was not examined due to arbitrary methodological reliability.

2.2.3. Eligibility criteria

We considered the most reliable study types according to the waterfall principle of the 6S Evidence Pyramid of Haynes and DynaMed [70,71]. Both retrospective and prospective studies were taken into account. Case reports, comments, reviews and technical notes were ignored.

Secondly, studies were screened on title and abstract, in which we focused on: "5-aminolevulinic acid", "recurrent", "protoporphyrine IX", "photosensitizing agents", "extent of resection", "Karnofsky Performance Scale", "overall survival", "progression-free survival", "safety", "intraoperative care", "fluorescence-guided surgery", "conventional white-light resection", "neuronavigation", "glioma surgery", "brain neoplasms", "high-grade glioma", "glioblastoma multiforme" and "malignant glioma". Studies that did not fit our research question, incomplete and duplicate studies were excluded.

Thirdly, all studies were subjected to our predetermined inclusion and exclusion criteria (Table 2). It should be noted that not only studies on GBM were considered, but other malignant tumors according to the 2016 World Health Organization classification as well.

Lastly, unlike other systematic reviews, we were especially interested in the evaluation of 5-ALA in recurrent HGG. Therefore, we excluded studies focusing exclusively on newly diagnosed HGG. Remaining studies were evaluated in full-text and checked in more detail.

2.2.4. Quality and risk of bias assessment

Quality assessment was performed according to the guidelines of the Enhancing the Quality And Transparency Of health Research network. Systematic reviews, diagnostic and cohort studies were evaluated according to the PRISMA-, STARD- and STROCSS-statement, respectively [72–74]. Since no randomised controlled trials were included, the Risk-Of-Bias-In-Non-randomised-Studies-of-Interventions (ROBINS-I) tool was used to evaluate the risk of bias [75]. Funnel plots were examined to detect publication bias [76]. Other forms of bias that were explicitly mentioned were also taken into account. Corresponding figures were made using Review Manager 5.3. We excluded studies that were not consistent with our quality assessment or those with an unacceptable risk of bias. All assessments can be obtained at any time by contacting the corresponding author without any costs attached.

2.2.5. Reference point

We searched for an appropriate reference point to compare 5-ALA in recurrent and newly diagnosed HGG. We used six systematic reviews that analysed 5-ALA usage in newly diagnosed HGG (Table 3). Checking ongoing literature yielded one additional systematic review that will be published soon [77]. The PRISMA-statement was used to make sure our reference point complied the highest amount of methodological reliability. The PRISMA-statement can be obtained at any time by contacting the corresponding author without any costs attached.

2.3. Statistical analysis

2.3.1. Database

An inventory database was created using data that could be

Table 1
PICO-model and PIRT-model.

Survival and safety		Diagnostic accuracy and extent of resection		
P	Patient	**P**	Patient	Recurrent high-grade glioma (WHO grade III or IV)
I	Intervention	**I**	Index test	5-aminolevulinic acid guided surgery + adjuvant chemotherapy and/or radiotherapy
C	Comparison	**R**	Reference test	➢ Conventional WLR + adjuvant chemotherapy and/or radiotherapy ➢ Newly diagnosed high-grade glioma (WHO grade III or IV)
O	Outcome	**T**	Target condition	Diagnostic accuracy, extent of resection, safety and survival

Table showing the PICO-model that was used for the objectives "survival" and "safety", as well as the PIRT-model that was used for "diagnostic accuracy" and "extent of resection". WHO = World Health Organization; WLR = White-Light Resection.

Table 2
Inclusion and exclusion criteria.

INCLUSION CRITERIA	EXCLUSION CRITERIA
• HGG (WHO grade III or IV) • Recurrent HGG • Brain neoplasms • 5-aminolevulinic acid guided surgery • Conventional white-light resection • Age 18 – 85 years	• Solely LGG • Solely newly diagnosed HGG • Other than brain neoplasms (e.g. metastases, abscess, cavernoma, aneurysm) • Solely radiotherapy or chemotherapy • Solely radiotherapy-chemotherapy • Pediatric population • Inappropriate STARD- or STROCCS-statement • Inappropriate ROBINS-I-tool • Duplicate records • Review / comment / report / technical note / in vitro study / animal study • Language other than English • Other photosensitizing agents than 5-aminolevulinic acid • Inaccessible databases

Table showing the inclusion and exclusion criteria. Studies that did not fulfil our inclusion criteria were excluded. HGG = High-Grade Glioma; LGG = Low-Grade Glioma; WHO = World Health Organization; STARD = Standards for Reporting Diagnostic Accuracy; STROCSS = Strengthening the Reporting of Cohort Studies in Surgery; ROBINS-I = Risk Of Bias In Non-randomised Studies of Interventions.

Table 3
Systematic review reference point.

Systematic review	Publication year	Number of included studies
Shiguang et al.	2013	10
Hadjipanayis et al.	2015	9
Eljamel et al.	2015	20
Ferraro et al.	2016	22
Mansouri et al.	2016	43
Senders et al.	2016	105

Table showing systematic reviews used as a reference point to compare results of 5-ALA in recurrent HGG.

retrieved directly from the included studies, as well as additional information extracted from the database of Mansouri et al. [21]. Irretrievable information was left blank, meaning that authors were not contacted in case of incomplete or missing data.

2.3.2. Meta-analysis

Due to obvious heterogeneity and methodological variability across included studies, we deliberately decided not to perform a meta-analysis. Another reason was the poor reporting of results encountered in some of the included studies (e.g. no clear description of how primary endpoints were measured). Pooling individual studies could therefore create misleading results.

3. Results

3.1. Study selection

The sequence of consecutive steps used in our systematic review is depicted by the QUORUM flow chart (Fig. 2) [78]. A total of eighteen studies met the final inclusion criteria [8,15,49,50,53,57,61–63,79–87]. 229 studies were excluded for reasons provided in Fig. 2.

3.2. Characteristics of included studies

Characteristics of included studies are summarised in Appendix D. All articles are written in English. Twelve and five studies are prospective and retrospective, respectively, while one study relates to a histological examination. All studies are unicentric, except for one. All studies are non-randomised. Our review encompasses two case-control studies [63,80], two single-arm uncontrolled phase II studies [57,62] and one systematic review [87]. Publication year and recruitment time varies from 2007 to 2018 and 2003 to 2018, respectively. Follow-up ranges from 6 to 43 months.

Patient characteristics, treatment protocols and additional tools are heterogeneous. In total, 552 grade IV, 146 grade III, 17 grade II, two transformations from a LGG and 19 MET are included. Of these, 455 newly diagnosed and 276 recurrent tumors are included. 1064 biopsy specimens were taken. Mean age varies from 22 to 63 years.

Fourteen studies provided a breakdown of sex ratios (370 males, 242 females). All patients received 20 mg/kg 5-ALA orally two to four hours preoperatively.

3.3. Risk of bias within included studies

3.3.1. Risk of bias in systematic reviews

We evaluated bias in systematic reviews concerning 5-ALA in newly diagnosed gliomas using the ROB-tool (Appendix B). Bias encountered was mostly inevitable. The study design did not allow for double-blinding, since neurosurgeons could not be blinded prior to surgery. Many studies did not mention any usage of random sequence generation. Therefore, this tool probably reflects an overestimation of the actual amount of bias.

3.3.2. Risk of bias in non-randomised studies

We evaluated bias in non-randomised studies concerning 5-ALA in recurrent gliomas using the ROBINS-I-tool (Appendix C.). Significant risk of selection bias was found in only one study, because three patients were excluded after start of intervention based on negative fluorescence [50]. Most studies did not report blinding of radiologists and pathologists. The adjustments that could have result into bias were explicitly stated prior to statistical analysis. Therefore, the overall risk of bias was substantial but anticipated and acceptable.

3.4. Diagnostic accuracy

Fourteen studies are reported on diagnostic accuracy in recurrent HGG [8,15,49,50,53,57,61–63,79,81,83,85,86]. Results are summarised in Appendix E. A comparison with newly diagnosed HGG is shown in Appendix I.

3.4.1. Sensitivity and specificity to detect tumor tissue

Although study designs are heterogeneous, most studies report an 80–85% sensitivity [8,53,61,62,79]. Two studies even report a 100% sensitivity, although one study only included three recurrent HGG [82,85]. When comparing fluorescence with conventional MRI-neuronavigation in regard to tumor boundary identification, most studies report superiority of 5-ALA in both newly diagnosed and recurrent tumors [4,82,83]. The added value is even higher in recurrent compared to newly diagnosed GBM [82,88]. One study indicates that a

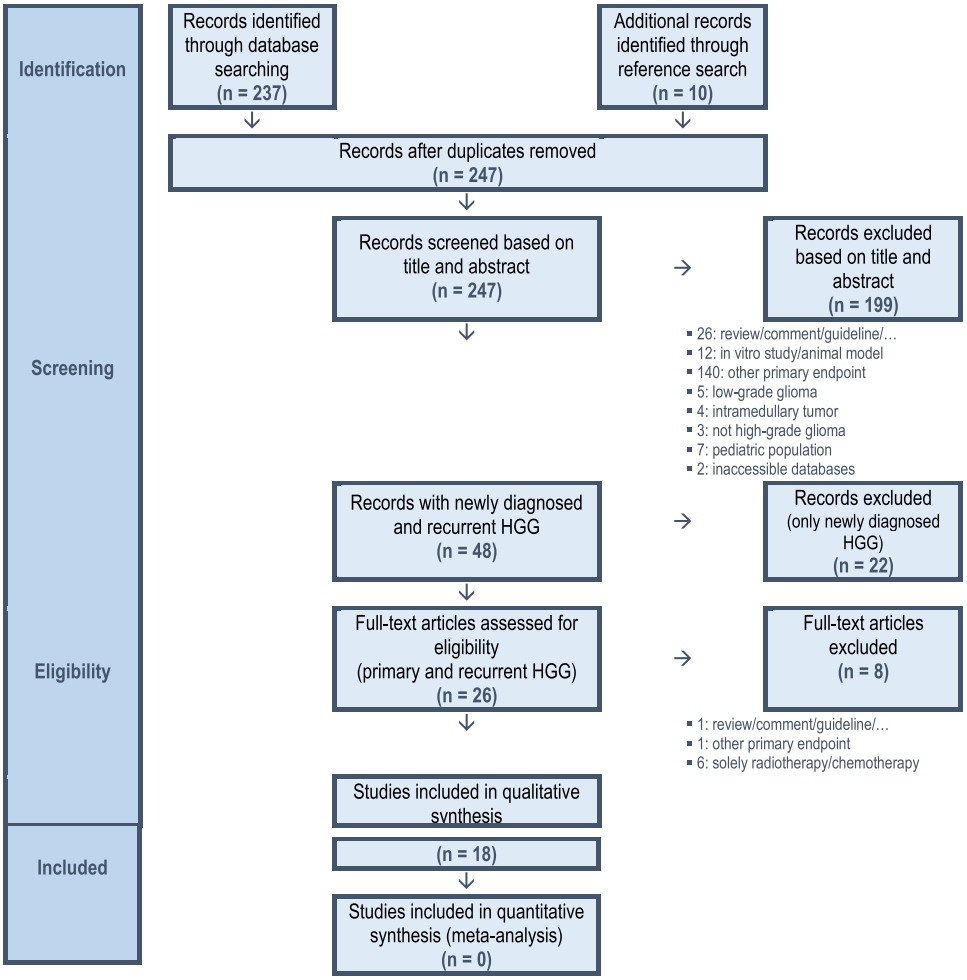

Fig. 2. The Quality of Reporting of Meta-analyses (QUORUM) flow chart illustrating the consecutive steps that were followed during our systematic review. Reasons for exclusion are also mentioned. HGG = High-Grade Glioma.

combination of 5-ALA and MRI-neuronavigation lowers sensitivity, but increases specificity [54].

Sensitivity seems higher in newly diagnosed HGG compared to recurrent HGG [83], although not every study confirms this statement [61]. Moreover, no randomised case-control trial has ever confirmed this tendency. Grade IV gliomas are more often fluorescent with respect to grade III gliomas [8], although not every study confirms this statement [61]. No significant difference in fluorescence was observed in gliomas that were provided with adjuvant treatment after primary surgery [8].

One prospective analysis examines differences between 5-ALA and 18F-FET-PET in HGG and LGG [86]. 18F-FET-PET sensitivity seems significantly higher than 5-ALA fluorescence. Therefore, as suggested by the authors, 5-ALA-guided resection should not be initiated in patients with negative 18F-FET-PET uptake. However, when examining recurrent gliomas in more detail, the sensitivity seems to be equal. It should be noted that 17 out of 30 patients suffered from a LGG, blurring the results. These results are in contrast to another study, in which 5-

- Administered 3–4 hours prior to anesthesia
- Adverse events are rare
- Radio-sensitizing effect
- Preferential accumulation in HGG not completely understood
- PPIX cannot cross intact BBB
- Accumulation in other tissues as well (LGG, choroid plexus, ependymoma etc.)
- Very limited amount of accumulation in normal brain tissue
- Removal of solid part has greatest impact on survival
- Intensity correlates well with tumor cellularity
- Absence of fluorescence not always indicative of tumor absence (e.g. photo-bleaching)
- Presence of fluorescence not always indicative of tumor presence (e.g. auto-fluorescence)
- 85% sensitivity (similar to newly diagnosed HGG)
- Lower specificity and NPV in recurrent HGG
- No impact of previous chemotherapy or radiotherapy
- Complementary to MRI-neuronavigation
- Significant impact on OS, not on PFS

Fig. 3. Summary of common clinical observations when using 5-aminolevulinic acid in the treatment of recurrent high-grade gliomas. HGG = High-Grade Glioma; PPIX = Protoporphyrin IX; BBB = Blood-Brain-Barrier; LGG = Low-Grade Glioma; NPV = Negative Predictive Value; OS = Overall Survival; PFS = Progression-Free Survival.

ALA seems more sensitive in predicting tumor remnants than 18F-FET-PET [49]. Timing was the main difference in both studies, in which 18F-FET-PET was performed preoperatively in the former, while post-operatively in the latter.

One prospective non-randomised study evaluates sensitivity and specificity of both 5-ALA and Gd-DTPA intraoperative MRI (iMRI) in HGG and brain MET [89]. When focusing on HGG, sensitivity of 5-ALA is significantly higher than iMRI. However, specificity shows opposite results. When focusing on brain MET, no differences concerning sensitivity and specificity can be obtained. Therefore, iMRI shows no additional advantages compared to 5-ALA in brain MET.

Multiple meta-analyses of newly diagnosed gliomas show sensitivities of 80–95% and specificities of 60–65% [4,5,90–93]. Therefore, sensitivities seem similar, while specificities seem higher in newly diagnosed gliomas [62]. However, it should be noted that most meta-analyses included both newly diagnosed and recurrent gliomas, blurring the results.

3.4.2. Positive and negative predictive value (PPV and NPV)

Most studies report a mean PPV of 90% [57,61,62]. PPV is higher in areas appearing pathological under white-light compared to areas that appear normal [57]. A correlation between PPV and fluorescence-intensity was found, in which areas with strong fluorescence show higher PPV as opposed to areas with weak fluorescence, both in newly diagnosed and recurrent gliomas [4,5,15,57,61–63,90–93]. Prior chemo- or radiotherapy did not alter PPV [38,57,85]. On the other hand, no fluorescence seems to have lower NPV in recurrent HGG [15,57,61–63]. Moreover, IDH1 and IDH2 mutations seem to be associated with low NPV, both in newly diagnosed and recurrent HGG [8,94]. PPV and NPV of 5-ALA and iMRI did not significantly differ [89]. When looking at 5-ALA in newly diagnosed gliomas, PPV and NPV amount to 90–100% and 40–50%, respectively [58,62,87]. While PPV in newly diagnosed and recurrent HGG (mean value of 93%) look similar, NPV of absence of fluorescence seems to be lower in recurrent HGG (mean value of 31%) [4,5,62,90–93]. Therefore, both in newly diagnosed and recurrent HGG, presence of strong fluorescence indicates a very high probability of tumor presence, while absence of fluorescence does not predictably indicates absence of tumor, especially in recurrent HGG.(62)

3.4.3. False positives and false negatives (FP and FN)

Absence of tumor cells in fluorescent tissue (FP), is more common in the tumor boundary compared to tumor bulk [53]. Moreover, FP is higher in recurrent (mean value of 35%) as opposed to newly diagnosed tumors [53,62]. It is fairly common in recurrent HGG and brain MET, but relatively rare in newly diagnosed HGG [53]. This could be the result of an intense infiltration of neutrophils, reactive astrocytes and macrophages after adjuvant therapies, as well as radiation necrosis [87]. Peritumoral edema probably plays an important role in brain MET. Absence of fluorescence in tumor tissue (FN) was rather high in recurrent gliomas (mean value of 62%) [62]. This could be reduced by combining 5-ALA and iMRI [79].

3.5. Extent of resection (EOR)

EOR in recurrent gliomas was assessed in eleven studies [8,15,57,61,63,79–82,84,85]. Results are summarised in Appendix F. A comparison with newly diagnosed HGG is shown in Appendix I. It should be noted that there is a high variability concerning criteria and intraoperative adjuvant tools between different studies, making a direct comparison delicate and should be done with caution.

3.5.1. Gross total resection (GTR)

GTR was most commonly defined as absence of contrast-enhancement on MRI within 72 h postoperatively [15,57,61,63,79–81]. Other studies defined GTR as contrast-enhancement $< 0.175\ cm^3$ [84], or $<$ 0.28 ml. [85]. Two studies accomplished GTR in all patients [79,85]. However, it should be noted that one study includes only three recurrent GBM, in which all patients received neoadjuvant radio- and chemotherapy. Other studies report lower rates, ranging from 19 to 89%. Lowest percentage is 19.4%. This was due to tumor infiltration in viable structures (e.g. pyramidal tract, corpus callosum, basal ganglia) [57]. Most meta-analyses on 5-ALA in newly diagnosed HGG show GTR of 83–94% [4,5,21,90–93]. As expected, GTR is lower in eloquent brain tumors, ranging from 64 to 74% [5,91]. Most studies report higher GTR in newly diagnosed with respect to recurrent gliomas, although not significantly [81]. However, one study shows a higher GTR in recurrent gliomas [15]. In this study, newly diagnosed GBM was defined as patients who underwent first resection or had previous biopsy or partial resection in another center, but no previous chemo- or radiotherapy. Another study used the same database and looked at mitotic index and nestin immunostaining [63]. A significant positive correlation between mitotic index and fluorescence was seen.

One study evaluates GTR in patients undergoing 5-ALA-guided microsurgery combined with iMRI, in which residual tumor was seen in 52% [61]. According to another study, focusing on newly diagnosed HGG, but methodologically criticized [95], iMRI is superior to 5-ALA regarding total resection rates, particularly in eloquently located tumors [96]. However, other studies conclude that 5-ALA and iMRI have synergistic effects in tumor resection [97,98]. Finally, different tumor grades showed no significant difference in GTR [81].

3.5.2. EOR > 98%

EOR > 98% was an objective frequently encountered [8,63,82]. Most studies report higher rates in newly diagnosed with respect to recurrent GBM, although one study shows opposite results [82]. This observation is not significant, however. There is a significant difference between grade III and grade IV HGG, with higher rates in the latter [82]. Although fluorescence improves EOR > 98% (58% vs. 50%), this was not significant [8]. Finally, EOR > 98% is not influenced by age or gender. [8].

3.6. Safety, adverse events (AE) and neurological outcome

Safety, AE and neurological outcome in recurrent HGG were assessed in thirteen studies [8,15,49,57,61–63,79–81,84–86]. Results are summarised in Appendix G. A comparison with newly diagnosed HGG is shown in Appendix I.

3.6.1. Postoperative new neurological deficits (PNND)

Overall amount of PNND ranged from 11 to 36%. Most of these were temporary, leading to a small percentage of permanent deficits. In one study, all gliomas with PNND showed fluorescence during microsurgery [8]. PNND are more often in grade IV with respect to grade III gliomas [8]. There is a positive correlation between EOR and prevalence of PNND [8]. Patients without PNND show longer PFS (7.8 vs. 4.6 months) and OS (13.5 vs. 11.1 months) [8]. Therefore, benefits of repeated surgery seem to subside when complications occur.

3.6.2. Adverse events (AE)

AE are defined as the combination of PNND and persistence of preoperative neurological deficits or non-neurological adverse events. Overall amount ranges from 7 to 58%. In one study, impaired speech and motor function were the most prevalent [57]. Other AE explicitly mentioned include: deteriorated hemianopia, status epilepticus, hemiparesis, leg paresis, dysphasia and fine motor skills impairment [15,79,84]. Most studies show no 5-ALA-related AE [57,81,86]. However, one study reports drug-related AE in four patients: nausea and vomiting (three patients) and photosensitivity (one patient) [61]. No relevant shifts in laboratory parameters associated with 5-ALA were detected [57]. One study shows no significant difference in AE between recurrent GBM treated with multimodal therapy (5-ALA-guided microsurgery followed by a combination of high dose brachytherapy and

Temozolomide) and Temozolomide alone [80]. Two studies even show no AE or declines in neurological status [49,86]. A combination of 5-ALA and 18F-FET-PET was used in these studies.

AE are higher in the recurrent as opposed to the newly diagnosed group, as was seen in meta-analyses [4,91,92]. However, PNND seem to be similar in both study groups [8,57]. First surgery is associated with a significant lower morbidity and higher postoperative KPS [81]. Therefore, indications for 5-ALA usage in recurrent surgery should be followed very strictly.

3.6.3. Karnofsky Performance Scale (KPS) and National Institutes of Health Stroke Scale (NIHSS)

The KPS is frequently used in order to compare pre- and post-operative neurological status [99]. Preoperative KPS ranges from 60 to 100%. In one study, only one patient shows a KPS deterioration, due to progression of arm paresis and psychomotor retardation [85]. It should be noted that only three patients were included in this study. NIHSS is another way to assess neurological outcome postoperatively. Meta-analyses show higher rates of deterioration 48 h after surgery in newly diagnosed gliomas compared to recurrent gliomas [92,93].

3.7. Survival

Five studies report on survival in recurrent HGG [8,15,57,79,80]. Results are summarised in Appendix H. A comparison with newly diagnosed HGG is depicted in Appendix I.

3.7.1. Overall survival (OS)

Most studies define OS as “time between surgery and death from any cause” or “date of last follow-up in case of no documentation of death” [57]. A non-significant difference between grade III (9.9 months) and grade IV (7.4 months) gliomas is seen in one study [57]. 5-ALA is associated with a significant increase in OS in retrospective series [8]. A correlation between resection rates and survival is observed, in which > 98% resection leads to a significant increase in OS [8].

However, subgroup analyses show that this only applies to grade IV gliomas and is not observed in grade III gliomas [8]. Kaplan-Meier survival analyses show a significant increase in OS in patients with GTR. As already noted, OS and PFS are influenced by PNND, which predisposes those patients to a lower OS and PFS [8]. One study compares multimodal treatment (5-ALA-guided microsurgery followed by concomitant high dose brachytherapy and Temozolomide) with Temozolomide alone in patients with recurrent GBM, in which OS increases with a multimodal treatment [80]. Recurrent gliomas have inherently less favourable OS and PFS [15]. This is confirmed by meta-analyses, in which newly diagnosed gliomas show an OS and PFS of 14–15 months and 5–9 months, respectively [4,90–93]. One meta-analysis shows a gain in OS of 4–6.2 months in newly diagnosed gliomas with respect to recurrent gliomas [90].

3.7.2. Progression-free survival (PFS)

Progression was most commonly defined according to the Response Assessment in Neuro-Oncology (RANO) criteria [100–102]. In recurrent HGG, 5-ALA seems to have a significant influence on OS, although it does not have an impact on PFS [8]. This is in contrast to newly diagnosed HGG, in which 5-ALA appears to have an influence on PFS, but not on OS [21]. However, this only applied to patients younger than 55 years, since older patients also experience an increase in OS. [21] GTR is associated with longer PFS, as with OS. Finally, PFS seems to be increased significantly when combining Temozolomide with other treatment modalities [80].

4. Discussion

To our knowledge, this article forms one of the first comprehensive systematic reviews evaluating benefits of 5-ALA in recurrent HGG concerning diagnostic accuracy, extent of resection, safety and survival. In this review, the benefits of 5-ALA in the treatment of recurrent HGG were evaluated based on eighteen included studies. Our conclusions are, to a great extent, in line with those encountered in the individual included studies, as well as the systematic review published by Chohan et al. [87].

In contrast to Eljamel et al., [83] we found that 5-ALA sensitivity seems similar in recurrent and newly diagnosed gliomas, although specificity was lower. It should be noted that most meta-analyses included both newly diagnosed and recurrent gliomas, blurring the results. Della Puppa et al. [82] and Tykocki et al. [85] showed sensitivities of 100%, although these studies only included a small amount of patients. In line with the findings of Floeth et al. [86], diagnostic accuracy of 5-ALA was comparable to 18F-FET-PET in recurrent gliomas, although the former seems superior in detecting tumor remnants, as stated by Roessler et al. [49]. Sensitivity of 5-ALA was higher compared to iMRI, although specificity was lower. However, false negative results of 5-ALA fluorescence can be reduced by combining 5-ALA and iMRI, as stated by Quick-Weller et al. [79]. Roder et al. [96] conclude that iMRI is superior to 5-ALA in the resection of eloquently located tumors, although Tsugu et al. [97] and Eyupoglu et al. [98] state that both techniques have synergistic effects. A positive correlation between the amount of fluorescence and PPV exists in both recurrent and newly diagnosed gliomas. PPV in recurrent and newly diagnosed gliomas is equal, although NPV is lower in the former. Even more in recurrent gliomas, 5-ALA has a significant advantage in identifying tumor boundaries over conventional MRI-neuronavigation. Sensitivity, specificity, PPV and NPV were not influenced by previous chemo- or radiotherapy. GTR seems higher in newly diagnosed gliomas, although insignificant. Resection rates did not significantly differ between tumor grades.

In contrast to the study of Yamada et al., [61] most studies showed no 5-ALA-related adverse events. Although PNND occurred equally in recurrent and newly diagnosed gliomas, total amount of adverse events was higher in recurrent gliomas. Fortunately, most PNND were temporary. Nevertheless, indications for recurrent surgery should be followed strictly. Although not significant, PNND were more common in grade 4 compared to grade 3 gliomas. Both in recurrent and newly diagnosed gliomas, PNND seem to decrease OS and PFS. Self-evidently, OS and PFS are less favourable in recurrent gliomas, although amount of resection is correlated with an increased survival rate in both groups. 5-ALA increases OS in recurrent gliomas, but has no impact on PFS. On the other hand, 5-ALA increases PFS in newly diagnosed gliomas, without altering OS.

Our review contains some limitations. Bias was inevitable in some of our studies. Due to the fact that only published studies and articles written in English were selected, selection bias was unavoidable. The study of Coburger et al. [50] showed significant risk of bias because three patients were excluded after the start of intervention based on negative fluorescence. Additionally, grey literature was not considered appropriate, leading to some publication bias. As a consequence of open label nature of treatment options (FGS or WLR), allocation bias and read-out related bias to the study group could not be ruled out. Not every patient received an equal design of treatment modalities, leading to unavoidable performance bias. Attrition bias was limited, since drop out and loss to follow-up was minimal.

Secondly, individual studies showed great amount of heterogeneity. Different doses in different preoperative time intervals, as well as different definitions for GTR were used.

No standardised scale for quantifying the amount of 5-ALA fluorescence is available [91]. Therefore, exact connotations of the vague descriptions “strong” and “weak fluorescence” can differ, making a comparison of diagnostic accuracy less reliable. This could be partially compensated by future use of spectroscopy or specialised algorithms to estimate the concentration of accumulated PPIX. These techniques are

not used in the included studies, announcing new investigations in future research. Data on survival rates are difficult to compare, due to different treatment modalities and adjuvant tools. Altogether, it should be noted that great caution should be taken when comparing individual studies regarding diagnostic accuracy, EOR, safety and survival.

Thirdly, some research questions were not explored. 5-ALA usage in LGG was not examined, although previous research has already accentuated limited sensitivities with respect to HGG [4]. Sensitivities can be increased by using fiber optic probes [103–105]. Cost-effectiveness was not considered a study objective, although this topic has already been described by other authors [106,107]. Finally, data regarding safety of re-administration of 5-ALA within a few days is not available.

Fourthly, due to limited amount of literature concerning 5-ALA usage in recurrent HGG, we were obliged to include a diverse combination of study designs.

Finally, although systematic reviews are generally accomplished by two authors lege artis, the search, selection and quality assessment was performed by only one author.

5. Conclusion

Based on the available literature, it can be stated that 5-ALA forms a useful intraoperative addition to the repertoire of recurrent glioma surgery. Diagnostic accuracy of 5-ALA is similar in newly diagnosed and recurrent HGG, although specificity and negative predictive value seem lower in the latter. Furthermore, it shows a significant advantage in identifying tumor boundaries over conventional MRI-neuronavigation. It should be noted that, due to a lack of RCT's in current literature and the unavoidable heterogeneity between included studies, results should be interpreted cautiously. In future research, additional randomised studies with a more extensive study population are desirable.

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Informed consent

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Transparency statement

The manuscript is an honest, accurate and transparent account of the study being reported. No important aspects of the study have been omitted.

Patient and public involvement statement

There was no patient and public involvement.

CRediT authorship contribution statement

Senne Broekx: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization. **Frank Weyns:** Resources, Supervision. **Steven De Vleeschouwer:** Conceptualization, Methodology, Resources, Supervision, Project administration.

Declaration of Competing Interest

The first author declares there is no conflict of interest. The senior authors (FW and SDV) are official teachers in Gliolan training courses and have performed consultancy tasks in the past for Medac GmbH and Lamepro, for which a fee was received.

Appendix A. Supplementary data

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