Neurosurgery - Cases and Reviews

CASE SERIES

How Does 5-Aminolevulinic Acid Affect Histopathological Grading, Extent of Resection and Survival in High-Grade Glioma?

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Abstract

High-grade gliomas are aggressive brain tumours with a poor prognosis. The current goal of treatment is to achieve maximum safe surgical resection as this improves survival. However, the infiltrative nature of this cancer makes it difficult to delineate healthy from pathological tissue. Therefore, complete resection is rarely achieved and there is a high rate of tumour recurrence. Additionally, misdiagnosis is common and results from unrepresentative tissue sampling. This can lead to the initiation of incorrect adjuvant therapies. Fluorescence-guided surgery with 5-aminolevulinic acid is becoming an increasingly popular practice to address these issues. A literature review was conducted to investigate whether 5-aminolevulinic acid use can lead to more accurate tissue diagnoses and improve the extents of resection and survival outcomes among high-grade glioma patients. Research suggests that strong tissue fluorescence after 5-aminolevulinic acid administration is highly predictive of solid tumour whereas weak fluorescence is non-specific and may represent areas of infiltrating cancer and anaplasia outside of the tumour centre. 5-aminolevulinic acid may be more sensitive than peri-operative MRI in demonstrating full tumour extent. Resections with 5-aminolevulinic are more complete than those without due to better tumour boundary delineation. The effects of 5-aminolevulinic acid may be enhanced with intra-operative MRI. Surgery with 5-aminolevulinic acid may offer a survival advantage, but larger trials are still required to quantify the impact.

Keywords

5-ALA, 5-aminolevulinic acid, Fluorescence-guided surgery, Glioma surgery

Introduction

Gliomas are primary brain tumours arising from glial cells of the central nervous system (CNS). The World Health Organization (WHO) grades gliomas based on malignant potential, as determined by histopathological features, on a scale from I-IV. Low-grade gliomas (LGG) are graded I to II. These tumours have lower malignant potential and can be cured by surgery. High-grade gliomas (HGG) are graded III to IV. Grade III tumours include most anaplastic subtypes whereas grade IV tumours are commonly referred to as glioblastoma multiforme (GBM). HGGs are malignant, incurable and yield a poor prognosis [1,2]. The median overall survival of a patient with HGG is approximately 18 months [3].

Research has shown that a greater extent of resection improves survival in HGG patients [4]. However, a complete resection of tumour remains challenging because it is difficult to differentiate tumour from normal tissue under standard white-light microscopy [5]. Neuronavigation is commonly used intra-operatively to aid in tumour resection. It involves obtaining an MRI scan prior to surgery that registers with the patient using either fiducials or patient surface anatomy, providing real-time visual guidance to the surgeon. However, there may be imprecision with patient registration resulting in inaccuracy of tumour location. Additionally, brain shift, the movement of the brain during surgery, can render neuronavigation up to several centimetres inaccurate [6]. Finally, there is

mounting evidence to suggest that full tumour extent is underestimated on contrast imaging, shedding doubt on the reliability of peri-operative scanning in achieving maximal surgical resection [7-9].

After surgery, it is imperative that correct adjuvant therapies are initiated as this has also been shown to positively impact survival [10]. The type of adjuvant therapy depends on tumour grade. Non-diagnostic samples represent up to 24% of all stereotactic HGGs biopsy specimens, once again resulting from inaccuracies with neuronavigation [11,12]. This may potentially lead to tumour under-grading and delayed initiation of correct adjuvant treatment [13]. To counter this, serial biopsies are often required but this is associated with an increased risk of morbidity and mortality. Intraoperative neuropathological assessment can also be used but is time-consuming and not widely available [14].

The use of 5-aminolevulinic acid (5-ALA) has shown promise in addressing these issues. 5-ALA is a natural metabolite in the haemoglobin metabolic pathway. When exogenous 5-ALA is administered orally pre-operatively, it acts as a pro-agent with excellent penetration of the BBB. It accumulates preferentially in malignant glial cells due to reduced levels of ferrochelatase (mitochondrial enzyme involved in the final stage of haem synthesis) as well as selective uptake by an ATP-binding cassette transporter (ABCB6). Once 5-ALA has accumulated intracellularly, it is metabolized into the fluorescent metabolite, protoporphyrin IX (PpIX). PpIX provides violet-red fluorescence when visualized under blue-violet light intra-operatively [13]. Fluorescence of cancer tissue can range from light pink to deep red depending on cellular density, tumour proliferation, neovascularity and BBB permeability. Generally, the denser the tumour tissue, the darker the fluorescence [15]. The practice of fluorescent-guided surgery (FGS) with 5-aminolevulinic acid has increased dramatically over the last decade. 5-ALA is now approved for use as an optical-imaging agent in Europe, Asia, Australia and most recently USA [16].

The surge in popularity can largely be attributed to a phase III randomized trial by Stummer, et al. which provided level 2b evidence that greater tumour resection and improved progression-free survival (PFS) can be achieved among HGG patients who undergo resection with 5-ALA compared to those undergoing conventional white-light resection [17]. Other papers have also shown that 5-ALA is able to identify tumour tissue with very high predictive values [18,19]. The aim of this review is to elucidate the evolving role 5-ALA in influencing the histopathological grading, extent of resection and survival outcomes in HGGs.

Methods

A literature search of the EBSCO database was conducted using the terms "5-ALA" OR "5-aminoevulinic acid" AND "glioma surgery". 222 studies were screened against the criteria below. Relevant studies were also attained from the references of screened papers. A total of 14 studies met the inclusion criteria and were included in the review.

Inclusion criteria

Studies were selected if they were published after 2005 and before July 2023 and whose primary outcome evaluated the role of 5-ALA, alone or in combination with other surgical adjuncts, in identifying representative tumor tissue or influencing the extent of resection (EOR) in adult patients with new or recurrent gliomas. Any survival outcomes reported in these papers were included in this review to help determine whether the use of 5-ALA impacts on survival. There were no restrictions regarding language published in, study timeframe or sample sizes.

Exclusion criteria

Articles were excluded if they involved letters to the editor, pediatric patients (< 18 years), did not have full-text access, described the use of 5-ALA in non-glioma or low grade-glioma surgery, were duplicates, case-reports, or animal studies.

Table 1: Characteristics of studies evaluating the clinical value of PpIX fluorescence in identifying representative HGG tissue, as defined by neuroimaging ± histopathological criteria, in stereotactic biopsies or resections of suspected high-grade brain tumours.

Study	Sample size	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Piquer, et al. [20]	8	73	100	63	100
Widhalm, et al. [11]	33	100	80	100	91.9
Von Campe, et al. [21]	13	100	100	100	100
Widhalm, et al. [8]	26	88	89	91	85
Coburger, et al. [7]	34	91	80	22	99
Stummer, et al. [19]	33	-	-	39.5	96.2
Roessler, et al. [9]	10	-	-	-	100
Díez Valle, et al. [18]	36	92.2	92.3	66.6	98.6

PpIX: Protoporphyrin IX; HGG: High-grade gliomas (WHO grade ≥ 3); NPV: Negative Predictive Value; PPV: Positive Predictive Value; Lggs: Low-Grade Gliomas

Table 2: Characteristics of studies evaluating the role of FGS with 5-ALA on extents of resection ± post-operative survival in HGGs.

Study	Population	Intervention	Control	% of patients who received CRET		Mean EoR (%)		Median survival since intervention (months)		Significant survival benefit vs. control (months)	
				Intervention	Control	Intervention	Control	OS	PFS	OS	PFS
Della Puppa, et al. [22]	HGGs in eloquent areas only	FGS with functional mapping and iMRI (N = 31)	-	74	-	98.9	-	-	-	-	-
Schatlo, et al. [23]	HGGs	FGS and iMRI (N = 55)	No iMRI (N = 145)	45	30	-	-	17.9	10.6	None	None
Sharma, et al. [24]	HGGs	FGS and iMRI (N = 37)	-	97.3	-	99.9	-	31.2	-	-	-
Quick-Weller, et al. [25]	Recurrent HGGs only	FGS and iMRI (N = 7)	-	100	-	100	-	7.6	-	-	-
Archavlis, et al. [26]	Recurrent HGGs only	FGS, brachytherapy and temozolamide chemotherapy (N = 17)	Temozolamide chemotherapy only (N = 17)	59	-	-	-	8	7	3	3.5
Coburger, et al. [27]	HGGs	FGS and iMRI (N = 33)	iMRI only (N = 33)	75.8	-	99.7	97.4	18	6	None	None
Díez Valle, et al. [18]	HGGs	FGS and iMRI (N = 36)	-	83.3	-	99.8	-	11.8	-	-	-
Piquer, et al. [20]	HGGs	FGS and iMRI (N = 27)	-	79.3	-	-	-	-	-	-	-

HGG: High-Grade Gliomas (WHO grade ≥ 3); FGS: Fluorescence-Guided Surgery (with 5-ALA); Imri: Intra-Operative MRI; CRET: Complete Resection of Enhancing Tumour; EoR: Extent of Resection; OS: Overall Survival from treatment; PFS: Progression-Free Survival (time between surgery and development of new symptoms or progression of tumour on imaging)

Results

Table 1 and Table 2.

Discussion

5-ALA can identify HGG tissue with very high PPV values thus reducing the chance of obtaining a negative biopsy. PPV correlates with the degree of fluorescence, such that stronger fluorescing areas are very likely to represent HGG tissue [7,8,11,18-21]. The reliability of strong PpIX fluorescence as a marker of cancer should provide surgeons performing stereotactic brain biopsies with enough confidence to take as few samples as possible from these sites to reduce procedure-related morbidity and maximize diagnostic yield. Strong PpIX fluorescence may also negate the need for intra-operative histopathology, thus helping to reduce overall procedure time and cost [11,20,21].

On the other hand, vaguely or non-fluorescing areas are much more non-specific, representing a range of possible tissue diagnoses including infiltrating tumour, LGG tissue, gliosis or radionecrosis [9,11,18,19,21,25]. In these cases, serial biopsies, intra-operative histopathology, and even iMRI are recommended for accurate tissue diagnosis [11,21]. However, the value of vague PpIX fluorescence should not be underestimated; these areas may represent tumour infiltration into normal tissue [18,19]. Surgeons can achieve a safe and "supramaximal" resection by resecting these areas if non-eloquent. If vague fluorescence extends into eloquent cortex, surgery could proceed cautiously with neurophysiological monitoring [18,22,25,27].

5-ALA has advantages over peri-operative MRI in accurately detecting representative HGG tissue. For example, Widhalm, et al. demonstrated a correlation between intra-operative PpIX fluorescence in diffusely infiltrating gliomas without significant contrast enhancement and degree of anaplasia [8]. Coburger, et al. demonstrated higher sensitivity and specificity of PpIX fluorescence in detecting residual HGG tissue at the border zone post-resection compared to iMRI [7]. Areas of residual tumour may act as foci for future tumour recurrence; without 5-ALA, these foci could be missed if iMRI is used alone [7-9]. Additional studies support the claim that 5-ALA is superior to contrast enhancement on post-operative MRI in detecting residual tumour [18,19].

On the other hand, Quick-Weller, et al. demonstrated that iMRI can identify recurrent HGG tissue that does not fluoresce with 5-ALA intra-operatively [25]. In another study by Coburger, et al., the group demonstrated a lower rate of residual PpIX fluorescence post HGG resection than post-operative contrast enhancement on MRI [27]. The implications of these studies are not to rely on one technique over the other; merely that both techniques can be used together, if possible, to maximize tumour identification [7,20,25,27,28]. This was demonstrated by Panciani, et al., who found improved sensitivity in detecting HGG tissue when 5-ALA and neuronavigation are used together [28].

Extent of resection with 5-ALA is greater in newly diagnosed and recurrent HGGs compared to those without [17,23,27,29]. This is because 5-ALA enhances tumour visualization to beyond what can be detected under conventional white-light microscopy or pre-operative contrast MRI [29-31]. In a meta-analysis involving 565 patients with GBM who had tumour resection with 5-ALA, Eljamel found a gross total resection (GTR) > 98% in 75.4% of patients [31]. This compares favourably to an expected GTR > 98% in less than 50% of those operated on under white-light microsurgery [31,32]. 5-ALA also maximizes resection of eloquent-area HGGs; however, these resections are still often sub-total due to risk of neurological injury [18,22,23,27,33]. Authors recommend combining 5-ALA use with other adjuncts such as neurophysiological monitoring, iMRI or awake surgery, as this increases chances of safely achieving CRET in newly diagnosed and recurrent HGGs [18,22-25,27]. Despite greater extents of resection with 5-ALA, post-operative morbidity and mortality does not seem to be significantly increased [9,18,20,22,24,27]. Moreover, 5-ALA is associated with no or only minor adverse effects such as thrombocytopoenia, a rise in liver enzymes, skin flushing and pruritis [8,20,24].

Greater extents of resection lead to improved overall survival in HGG patients. Although 5-ALA leads to greater extents of resection, meta-analyses have demonstrated only modest survival benefits with 5-ALA [5,31]. This is likely due to an abundance of low-quality evidence with small sample sizes. Larger randomized-control studies focusing on post-operative survival are required to quantify any meaningful effect of 5-ALA on survival [5,18,22,26,27].

Conclusion

5-ALA in FGS is a safe and practical method of visualizing HGG tissue in real-time that is independent of brain-shift. Strong PpIX fluorescence is highly predictive of HGG tissue, whereas vague fluorescence may suggest cancer tissue outside of the tumour centre. Importantly, 5-ALA can pick up on tumour foci showing no obvious contrast enhancement on MRI. The implications of this are more representative tissue sampling and extended tumour resections compared to surgery without 5-ALA. These effects may be augmented when used alongside intra-operative MRI. The greater resections with 5-ALA may offer some survival advantage; larger studies are required to quantify this measure.

Declarations

Funding

Conflict of interest

The author does not have relevant financial or non-financial interests to disclose.

Ethics approval

No animal or human subjects were involved with this paper.

Data availability

The data reported in the tables is available from the corresponding full-text articles. No new data were created, analysed, or stored in a repository in this study.

Author contributions

All work was conducted by the sole author VS.

References

1. Stupp R, Brada M, van den Bent MJ, Tonn JC, Pentheroudakis G, et al. (2014) High-grade glioma: ESMO Clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 25: 93-101.

2. Hanif F, Muzaffar K, Perveen K, Malhi SM, Simjee SU (2017) Glioblastoma multiforme: A review of its epidemiology and pathogenesis through clinical presentation and treatment. Asian Pac J Cancer Prev 18: 3-9.

3. Noiphithak R, Veerasarn K (2017) Clinical predictors for survival and treatment outcome of high-grade glioma in Prasat Neurological Institute. Asian J Neurosurg 12: 28-33.

4. Brown TJ, Brennan MC, Li M, Church EW, Brandmeir NJ, et al. (2016) Association of the extent of resection with survival in glioblastoma: A systematic review and meta-analysis. JAMA Oncol 2: 1460-1469.

5. Gandhi S, Tayebi Meybodi A, Belykh E, Cavallo C, Zhao X, et al. (2019) Survival outcomes among patients with high-grade glioma treated with 5-aminolevulinic acid-guided surgery: A systematic review and meta-analysis. Front Oncol 9: 620.

6. Nimsky C, Ganslandt O, Cerny S, Hastreiter P, Greiner G, et al. (2000) Quantification of, visualization of, and compensation for brain shift using intraoperative magnetic resonance imaging. Neurosurgery 47: 1070-1080.

7. Coburger J, Engelke J, Scheuerle A, Thal DR, Hlavac M, et al. (2014) Tumor detection with 5-aminolevulinic acid fluorescence and Gd-DTPA-enhanced intraoperative MRI at the border of contrast-enhancing lesions: A prospective study based on histopathological assessment. Neurosurg Focus 36: E3.

8. Widhalm G, Kiesel B, Woehrer A, Traub-Weidinger T, Preusser M, et al. (2013) 5-Aminolevulinic acid induced fluorescence is a powerful intraoperative marker for precise histopathological grading of gliomas with non-significant contrast-enhancement. PLoS One 8: e76988.

9. Roessler K, Becherer A, Donat M, Cejna M, Zachenhofer I (2012) Intraoperative tissue fluorescence using 5-aminolevolinic acid (5-ALA) is more sensitive than contrast MRI or amino acid positron emission tomography ((18)F-FET PET) in glioblastoma surgery. Neurol Res 34: 314-317.

10. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, et al. (2005) European organisation for research and treatment of cancer brain tumor and radiotherapy group. National cancer institute of canada clinical trials group.

11. Widhalm G, Minchev G, Woehrer A, Preusser M, Kiesel B, et al. (2012) Strong 5-aminolevulinic acid-induced fluorescence is a novel intraoperative marker for representative tissue samples in stereotactic brain tumor biopsies. Neurosurg Rev 35: 381-391.

12. Jackson RJ, Fuller GN, Abi-Said D, Lang FF, Gokaslan ZL, et al. (2001) Limitations of stereotactic biopsy in the initial management of gliomas. Neuro-Oncology 3: 193-200.

13. Hadjipanayis CG, Widhalm G, Stummer W (2015) What is the surgical benefit of utilizing 5-aminolevulinic acid for fluorescence-guided surgery of malignant gliomas? Neurosurgery 77: 663-673.

14. Dammers R, Schouten JW, Haitsma IK, Vincent AJ, Kros JM, et al. (2010) Towards improving the safety and diagnostic yield of stereotactic biopsy in a single centre. Acta Neurochir 152: 1915-1921.

15. Stummer W, Reulen HJ, Novotny A, Stepp H, Tonn JC (2003) Fluorescence-guided resections of malignant gliomas--an overview. Acta Neurochir 88: 9-12.

16. Hadjipanayis CG, Stummer W (2019) 5-ALA and FDA approval for glioma surgery. J Neurooncol 141: 479-486.

17. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, et al. (2006) Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: A randomised controlled multicentre phase III trial. Lancet Oncol 7: 392-401.

18. Diez Valle R, Tejada Solis S, Idoate Gastearena MA, Garcia de Eulate R, Dominguez Echavarri P, et al. (2011) Surgery guided by 5-aminolevulinic fluorescence in glioblastoma: Volumetric analysis of extent of resection in single-center experience. J Neurooncol 102: 105-113.

19. Stummer W, Tonn JC, Goetz C, Ullrich W, Stepp H, et al. (2014) 5-Aminolevulinic acid-derived tumor fluorescence: the diagnostic accuracy of visible fluorescence qualities as corroborated by spectrometry and histology and postoperative imaging. Neurosurgery 74: 310-320.

20. Piquer J, Llacer JL, Rovira V, Riesgo P, Rodriguez R, et al. (2014) Fluorescence-guided surgery and biopsy in gliomas with an exoscope system. Biomed Res Int 2014: 207974.

21. von Campe G, Moschopulos M, Hefti M (2012) 5-Aminolevulinic acid-induced protoporphyrin IX fluorescence as immediate intraoperative indicator to improve the safety of malignant or high-grade brain tumor diagnosis in frameless stereotactic biopsies. Acta Neurochir 154: 585-588.

22. Della Puppa A, De Pellegrin S, d'Avella E, Gioffre G, Rossetto M, et al. (2013) 5-aminolevulinic acid (5-ALA) fluorescence guided surgery of high-grade gliomas in eloquent areas assisted by functional mapping. Our experience and review of the literature. Acta Neurochir 155: 965-972.

23. Schatlo B, Fandino J, Smoll NR, Wetzel O, Remonda L, et al. (2015) Outcomes after combined use of intraoperative MRI and 5-aminolevulinic acid in high-grade glioma surgery. Neuro-Oncology 17: 1560-1567.

24. Sharma V, Kedia R, Narang KS, Jha AN (2018) Enhanced resection of primary high-grade gliomas using a combination of intraoperative magnetic resonance imaging and intraoperative fluorescence (5-aminolevulinic acid): A single-centre experience. Neurol India 66: 747-752.

25. Quick-Weller J, Lescher S, Forster MT, Konczalla J, Seifert V, et al. (2016) Combination of 5-ALA and iMRI in re-resection of recurrent glioblastoma. Br J Neurosurg 30: 313-317.

26. Archavlis E, Tselis N, Birn G, Ulrich P, Zamboglou N (2014) Salvage therapy for recurrent glioblastoma multiforme: A multimodal approach combining fluorescence-guided resurgery, interstitial irradiation, and chemotherapy. Neurol Res 36: 1047-1055.

27. Coburger J, Hagel V, Wirtz CR, Konig R (2015) Surgery for glioblastoma: Impact of the combined use of 5-aminolevulinic acid and intraoperative MRI on extent of resection and survival. PLoS One 10: e0131872.

28. Panciani PP, Fontanella M, Garbossa D, Agnoletti A, Ducati A, et al. (2012) 5-aminolevulinic acid and neuronavigation in high-grade glioma surgery: Results of a combined approach. Neurocirugia (Asturias, Spain) 23: 23-28.

29. Nabavi A, Thurm H, Zountsas B, Pietsch T, Lanfermann H, et al. (2009) Five-aminolevulinic acid for fluorescence-guided resection of recurrent malignant gliomas: A phase ii study. Neurosurgery 65: 1070-1077.

30. Schucht P, Knittel S, Slotboom J, Seidel K, Murek M, et al. (2014) 5-ALA complete resections go beyond MR contrast enhancement: Shift corrected volumetric analysis of the extent of resection in surgery for glioblastoma. Acta Neurochir 156: 305-312.

31. Eljamel S (2015) 5-ALA Fluorescence image guided resection of glioblastoma multiforme: A meta-analysis of the literature. Int J Mol Sci 16: 10443-10456.

32. Sanai N, Berger MS (2008) Glioma extent of resection and its impact on patient outcome. Neurosurgery 62: 753-764.

33. Feigl GC, Ritz R, Moraes M, Klein J, Ramina K, et al. (2010) Resection of malignant brain tumors in eloquent cortical areas: A new multimodal approach combining 5-aminolevulinic acid and intraoperative monitoring. J Neurosurg 113: 352-357.