MOH/P/PAK/505.23(TR)-e

TECHNOLOGY REVIEW (MINI-HTA)

5-AMINOLEVULINIC ACID (5-ALA) FOR BRAIN TUMOUR SURGICAL PROCEDURE

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
002/2021

IPT Mark
Mini-HTA
INAHTA

DISCLAIMER

This technology review (mini-HTA) is prepared to assist health care decision-makers and health care professionals in making well-informed decisions related to the use of health technology in health care system, which draws on restricted review from analysis of best pertinent literature available at the time of development. This technology review has been subjected to an external review process. While effort has been made to do so, this document may not fully reflect all scientific research available. Other relevant scientific findings may have been reported since the completion of this technology review. MaHTAS is not responsible for any errors, injury, loss or damage arising or relating to the use (or misuse) of any information, statement or content of this document or any of the source materials.

Please contact htamalaysia@moh.gov.my if further information is required.

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Government Office Complex
62590, Putrajaya
Tel: 603 8883 1229

Available online via the official Ministry of Health Malaysia website: http://www.moh.gov.my

e ISBN 978-967-2887-48-5

SUGGESTED CITATION: Maharita AR and Izzuna MMG. 5-Aminolevulinic Acid (5-ALA) for Brain Tumour Surgical Procedure. Technology Review. Ministry of Health Malaysia: Malaysian Health Technology Assessment Section (MaHTAS); 2021. 83 p. Report No.: 002/2021

DISCLOSURE: The author of this report has no competing interest in this subject and the preparation of this report is entirely funded by the Ministry of Health Malaysia.

Prepared by

Main-author (*Systematic Review)*:
Puan Maharita Ab Rahman
Pharmacist
Senior Principle Assistant Director
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Co-author *(Economic Evaluation)*:
Dr. Foo Sze Shir
Senior Principle Assistant Director
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Reviewed by

Dr. Izzuna Mudla Mohamed Ghazali
Public Health Physician
Deputy Director
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

External reviewer(s)

Dr. Liew Boon Seng
Neurosurgeon
Department of Neurosurgery
Hospital Sungai Buloh, Selangor

EXECUTIVE SUMMARY

Background

Brain tumour is a growth of malignant cells in brain tissue and the tumour that start in the brain is called primary brain tumour. The brain tumour is diagnosed through neurologic examinations and tests including with magnetic resonance imaging (MRI), CT-scan and biopsy. World Health Organisation's Globocan 2012 database reported that a total number of 786 cases of brain BT and cancers were reported in Malaysia; representing 2.1% of all reported cancers of the same year. In latest Malaysian National Cancer Registry Report (MNCRR) 2012-2016, a total number of brain tumour cases reported among Malaysian were 2,097 cases.

Although brain tumour still considered as an uncommon cancer in Malaysia compared to the other types of cancers (representing 1.95% of all malignancies in Malaysia), it is the most vivid form of human diseases, and the most promptly fatal type of cancers. The most common types of brain tumour among adults in Malaysia between 2011 to 2018 were meningioma and glioma which were reported in two local studies by Balqis N et. al. and Othman AK et. al.

Treatment options for brain tumour include surgery, radiation therapy, chemotherapy and targeted therapy. Instead of single therapy, many patients underwent combination therapies. However, removing the brain tumour can be challenging for the surgeons because it is difficult to see the difference between the tumour and healthy brain tissue especially with conventional surgery using white-light. Another alternative is fluorescence guide surgery (FGS) that used fluorescent agents which also known as fluorophores that fluoresce the tumour tissue under special light and guide the surgeon during tumour tissue resection to maximize extent of resection. There are limited number of fluorophores currently used in clinical practice and of it is 5-aminolevulinic acid (5-ALA). Fluorescence guided resection of malignant gliomas using 5-ALA was first approved in 2007 by the European Medical Agency, and in 2013 by the Pharmaceutical Affairs of Japan. Since then, this procedure has been widely used in clinical settings. In 2017, it was also approved by the Food and Drug Administration of the United States of America. In Japan, fluorescence-guided surgery for bladder cancer was also approved as an additional indication in 2017.

This technology review was requested by neurosurgeon from Hospital Tengku Ampuan Afzan, Ministry of Health (MOH) in order to assess the efficacy, safety and cost-effectiveness of 5-ALA in patients as the 5-ALA is not readily available for all Neurosurgical centres in MOH.

Objective/ aim

To assess the efficacy/effectiveness, safety and cost-effectiveness of 5-ALA in brain tumour surgery.

Results and conclusions:

Search results

A total of **135** records were identified through the Ovid interface and PubMed while **10** were identified from references of retrieved articles. After removal of duplicates and irrelevant titles, **106** titles were found to be potentially relevant and were screened using the inclusion and exclusion criteria. Of these, **45** relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria, **14** studies were included while **31** studies were excluded since the studies were already included in the SRs (n=20), narrative reviews (n=4), case reports/animal studies/laboratory studies (n=4) and other types of intra-operative surgeries (n=3). **The 14** full text articles finally selected for this review comprised of five systematic review, one RCT, six cohort studies and two case-control studies.

Conclusions

Based on the review 5-ALA improved progression free survival (PFS), gross total resection (GTR) and overall survival (OS) as compared to conventional treatment or white light surgery in high grade glioma (HGG). However, when compared with iMRI and fluorescein sodium, the difference was not significant. There was no difference in the outcome measure with low- or high-dose of 5-ALA. Overall, the used of 5-ALA was safe although there were a few incidence of transient elevation of liver enzymes and skin sensitivity which later on resolved without further treatment. On the economic side, 5-ALA have a potential of cost-effective as compared to white-light microscopy for HGGs. As for financial implication, the neurosurgical centre with the existing microscope system for 5-ALA will incur additional cost of RM6,800 per patient per year. Meanwhile, the neurosurgical centre with newly set-up microscope system for 5-ALA will require the treatment cost per patient per year range from RM13 000 to RM72 000.

Methods

The following electronic databases were searched through the Ovid interface:

- MEDLINE® In-Process and Other Non-Indexed Citations and Ovid MEDLINE® 1946 to March 2022

Other databases:

- PubMed
- Other websites: US FDA, INAHTA, CADTH

General databases such as Google and Google Scholar were used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles. The search was limited to articles on human. There was no language limitation in the search. **Appendix 1** showed the detailed search strategies. The last search was conducted on March 2021.

TABLE OF CONTENTS

ABBREVIATIONS

GTR	Gross-total resection
FGS	Fluorescence guide surgery
iMRI	Intraoperative magnetic resonance imaging
MNCRR	Malaysian National Cancer Registry
HGG	High grade glioma
LGG	Low grade glioma
5-ALA	5-Aminolevulinic acid
PpIX	Protoporphyrin
BBB	Blood brain barrier
EOR	Extent of resection
iOUS/iUS	Intraoperative ultrasound
GBM	Gliobastoma multiforme

1.0 BACKGROUND

Brain tumour is a growth of malignant cells in brain tissue and the tumour that start in the brain is called primary brain tumour. Meanwhile, tumour that spread to the brain is called metastatic brain tumour.[1] Brain tumour is diagnosed through neurologic examinations and tests including with magnetic resonance imaging (MRI), CT-scan and biopsy.[2]

A Global Burden of Disease Study (1990-2017) reported a total number of 405,000 cases of brain tumour worldwide with the total deaths related to the tumour was 247,000 cases. As for Malaysia, data from the World Health Organisation's Globocan 2012 reported a total number of 786 cases of brain tumour and brain cancers which represented 2.1% of all reported cancers of the same year. According to the latest Malaysian National Cancer Registry Report (MNCRR) 2012-2016, a total number of 2,097 cases of brain tumour among Malaysians which comprised of 1,117 cases among males and 908 cases among females were reported.[3]

In Malaysia, brain tumour is still considered as an uncommon cancer compared to the other types of cancers which was 1.95% of all malignancies in Malaysia. However, brain tumours are the most vivid form of human diseases, and the most promptly fatal type of cancers.[4] A study published in 2017 by Balqis N et. al. found that among 2017 brain tumour cases treated in Hospital Universiti Sains Malaysia between 2011 and 2014, the most common adult primary brain tumour was meningioma (32.7%) followed with glioblastoma (7.8%). According to age factor, brain tumour distribution pattern showed an increasing trend as the age increases. Furthermore, meningioma is the most common among the elderly. The study also mentioned that secondary tumour takes more than 10% from overall percentage of brain tumour cases.[4] Another study by Othman AK et. al. included 368 new cases of brain tumour from 2013 to 2018 in Hospital Sultanah Nurzahirah, found meningioma has the highest incidence (27.2%) followed by metastases brain tumour (18.1%) and glioma (17.4%).[3]

There are various treatment options for brain tumour including surgery, radiation therapy, chemotherapy and targeted therapy. Instead of single therapy, many patients underwent combination therapies.[2] However, removing the brain tumour can be challenging for the surgeons because it is difficult to see the difference between the tumour and healthy brain tissue.[5] Under conventional white light, most neurosurgeons have difficulty achieving maximum tumour resection without causing new neurological deficit due to the invasive and infiltrative nature of high-grade gliomas (HGGs).[6] The HGGs are a type of fast-growing brain tumour that can invade nearby brain tissue.[5]

Another alternative is fluorescence guide surgery (FGS) that used fluorescent agents which also known as fluorophores that fluoresce the tumour tissue under special light and guide the surgeon during tumour tissue resection to maximize extent of resection. There are limited number of fluorophores currently used in clinical practice and of it is 5-aminolevulinic acid (5-

ALA).[7] Fluorescence guided resection of malignant gliomas using 5-ALA was first approved in 2007 by the European Medical Agency, and in 2013 by the Pharmaceutical Affairs of Japan. Since then, this procedure has been widely used in clinical settings. In 2017, it was also approved by the Food and Drug Administration of the United States of America. In Japan, fluorescence-guided surgery for bladder cancer was also approved as an additional indication in 2017.[8]

This technology review was requested by a neurosurgeon from Hospital Tengku Ampuan Afzan, Ministry of Health (MOH) in order to assess the efficacy, safety and cost-effectiveness of 5-ALA in patients as the 5-ALA is not readily available in all Neurosurgical centres in MOH.

2.0 OBJECTIVE / AIM

To assess the efficacy/effectiveness, safety and cost-effectiveness of 5-ALA in brain tumour surgery.

3.0 TECHNICAL FEATURES

3.1 5-Aminolevulinic Acid

5-aminolaevulinic acid hydrochlorite/chloride (5-ALA) is a prodrug that is metabolised intracellularly to form protoporphyrin (PpIX) (molecule that is fluorescent). The fluorescent molecule accumulated in glioma tissue due to local disruption of the blood-brain-barrier (BBB) and increased PpIX synthesis by tumour cells. The PpIX fluorescence appears red within the tumour core and pink at the margins of lower concentrations of PpIX. The fluorescent helps the surgeons to see the tumour during surgery and guide its removal.[6,9]

The 5-ALA will be administered 3-hours before induction, then the areas within the tumour will glow pink or red, and healthy brain tissue appears blue when exposed to a special blue light during surgery. The PPIX will accumulates selectively in tumour cells (intracranial) which facilitated maximal removal of tumour and is associated with better outcome.[5,6,10]

The United State Food and Drug Administration (USFDA) has approved standards protocols /or dosing and timing of 5-ALA administration before intraoperative use for newly diagnosed high grade glioma (HGG). The protocols stated for 5-ALA dose of 20 mg/kg dissolved in 50 mL of water for oral administration.[11] Figure 1 showed a visual difference between conventional white-light surgical microscope and under violet-blue excitation light after 5-ALA ingestion.[12]

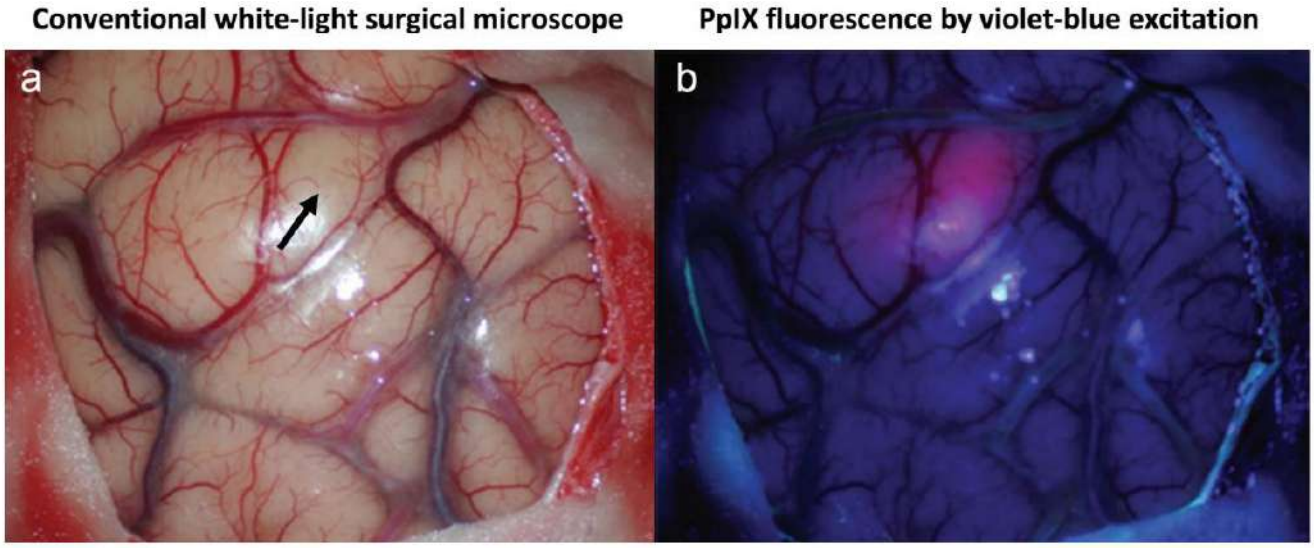

Figure 1: Visualization of tumour tissue of a malignant glioma (WHO grade IV) by using 5-ALA during fluorescence-guide tumour resection (the arrow is pointing to the tumour area)

a) By using the conventional white-light source
b) By switching the microscope to violet-blue excitation light, the glioma tissue can be clearly visualized by strong PpIX fluorescence

3.2 Other alternatives

There are a few fluorophores available and used in brain tumour resection. Those fluorophores are:[9, 7]

a) Not tumour-specific fluorophore (lack of molecular target)

- Indocyanine Green (ICG)
  Although not specifically approved for glioma surgery, used of ICG is to enhance extent of resection (EOR) during glioma resection. The ICG is a hydrophobic cyanine dye that binds to plasma proteins and typically remains in intravascular spaces is commonly used in angiography and cerebrovascular surgery

- Fluorescein Sodium
  Fluorescein was the first fluorophore used in fluorescence guided surgery (FGS). Under a 560-nm wavelength fluorescent light, the gliomas appear bright yellow. It has been used to enhance EOR and improve rate of gross total resection (GTR) in glioma resection. The fluorescein can be used in conjunction with 5-ALA

b) Tumour-specific fluorophore

- Tozuleristride
  Tozuleristride is a protein/fluorophore conjugate that uses ICG as fluorescent molecule bound to chlorotoxin that allows the conjugate to bind selectively to solid tumours

- Cancer-selective alkylphosphocholine analogs
  The cancer-selective alkylphosphocholine analogs conjugated with a green or near-infrared fluorophore. The compounds accumulated in tumour cell membranes due to increase number of lipid rafts

- Fluorescently labelled antibodies
  Cetuximab-IRDye800 is an antibody against EGFR commonly expressed in glioblastoma multiforme (GBM)

The FGS is frequently used in conjunction with intraoperative imaging techniques and / or neuro-monitoring to further enhance EOR while preventing post-operative neurological deficits.[9] Those imaging technologies includes:

- Intraoperative magnetic resonance imaging (iMRI): 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.[10] The iMRI can be used in conjunction with FGS to evaluate the residual tumour and enhance EOR.[9]

- Intraoperative ultrasound (iUS/iOUS):
  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.[10] The iUS provide real time visualisation of tumour with information on surrounding anatomy.[9]

4.0 METHODS

4.1 SEARCHING

Literature search was conducted by the author and with help of an *Information Specialist* who searched for full text articles.

The following electronic databases were searched through the Ovid interface:

- MEDLINE® In-Process and Other Non-Indexed Citations and Ovid MEDLINE® 1946 to March 2022

Other databases:

- PubMed
- Other websites: US FDA, INAHTA, CADTH

General databases such as Google and Google Scholar were used to search for additional web-based materials and information. Additional articles retrieved from reviewing the

bibliographies of retrieved articles. The search was limited to articles on human. There was no language limitation in the search. **Appendix 1** showed the detailed search strategies. The last search was conducted on March 2021.

4.2 SELECTION

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria. Relevant articles were then critically appraised using *Critical Appraisal Skills Programme (CASP) checklist* and graded according to *US/ Canadian Preventive Services Task Force* (**Appendix 2**). RoB 2 is used to assess risk of bias in RCT. Data were extracted and summarised in evidence table as in **Appendix 3**.

The inclusion and exclusion criteria were:

Inclusion criteria:

a.	**Population**	Patients who were diagnosed with brain tumour
b.	**Intervention**	5-aminolevulinic acid (5-ALA)
c.	**Comparator**	i. Conventional surgery
d.	**Outcomes**	i. Safety ii. Efficacy and effectiveness iii. Cost-effectiveness
e.	**Study design**	Systematic review, cohort, RCT, non-randomised control trial
f.	Full text articles published in English	

Exclusion criteria:

a.	**Study design**	animal study, case study, case report/case series
b.	Non English full text articles	

5.0 RESULTS

Search results

An overview of the search is illustrated in **Figure 2**. A total of **135** records were identified through the Ovid interface and PubMed while **10** were identified from references of retrieved articles. After removal of duplicates and irrelevant titles, **106** titles were found to be potentially relevant and were screened using the inclusion and exclusion criteria. Of these, **45** relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria, **14** studies were included while **31** studies were excluded since the studies were already included in the SRs (n=20), narrative reviews (n=4), case reports/animal studies/laboratory studies (n=4) and other types of intra-operative surgeries (n=3). **The 14** full text articles finally selected for this review comprised of five systematic review, one RCT, six cohort studies and two case-control studies. The studies were conducted in Korea, Denmark, Malaysia, France, Spain and Portugal.

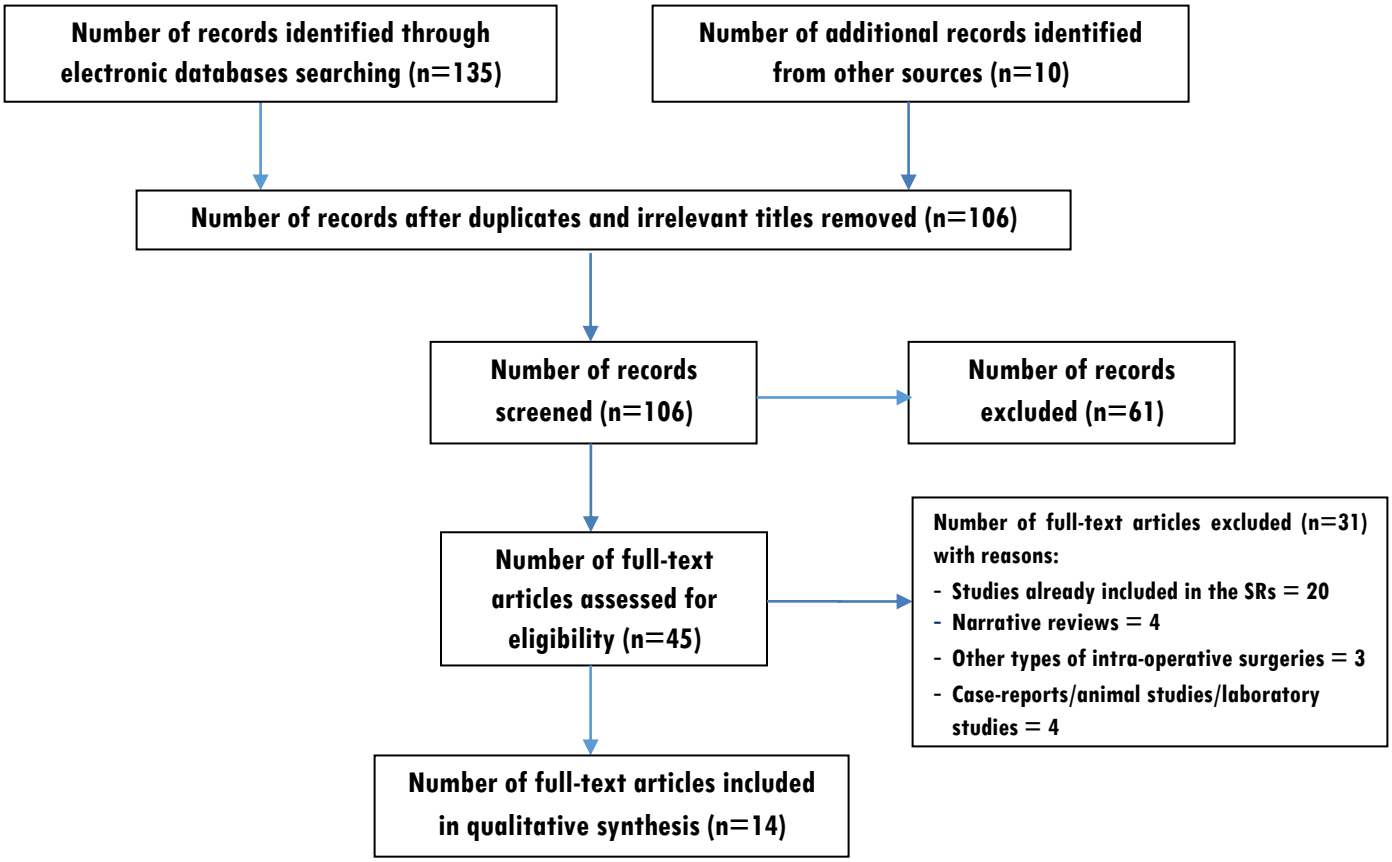

Figure 2: Flow chart of retrieval of articles used in the results

Quality assessment of the studies

The risk of bias in the included studies were assessed using domain-based evaluation adapted from the CASP checklist. This is achieved by answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias as either:

Overall, the risk of bias was low for the SRs. However, the SRs included variation of study types from observational and interventional studies depending on their objectives. Two SRs conducted network-meta analysis (NMA) as no direct comparison study available on the interventions of interest. Although the RCT was low in risk of bias, the sample size was small and for the non-RCT the control group was not reported. On the other hand, one case-control study does not really concern on other possibility of confounding factors especially on the other medication taken by the patients which might affect the outcome of the study. The results of risk of bias of the included studies are summarised in **Figure 3.1 and 3.5**

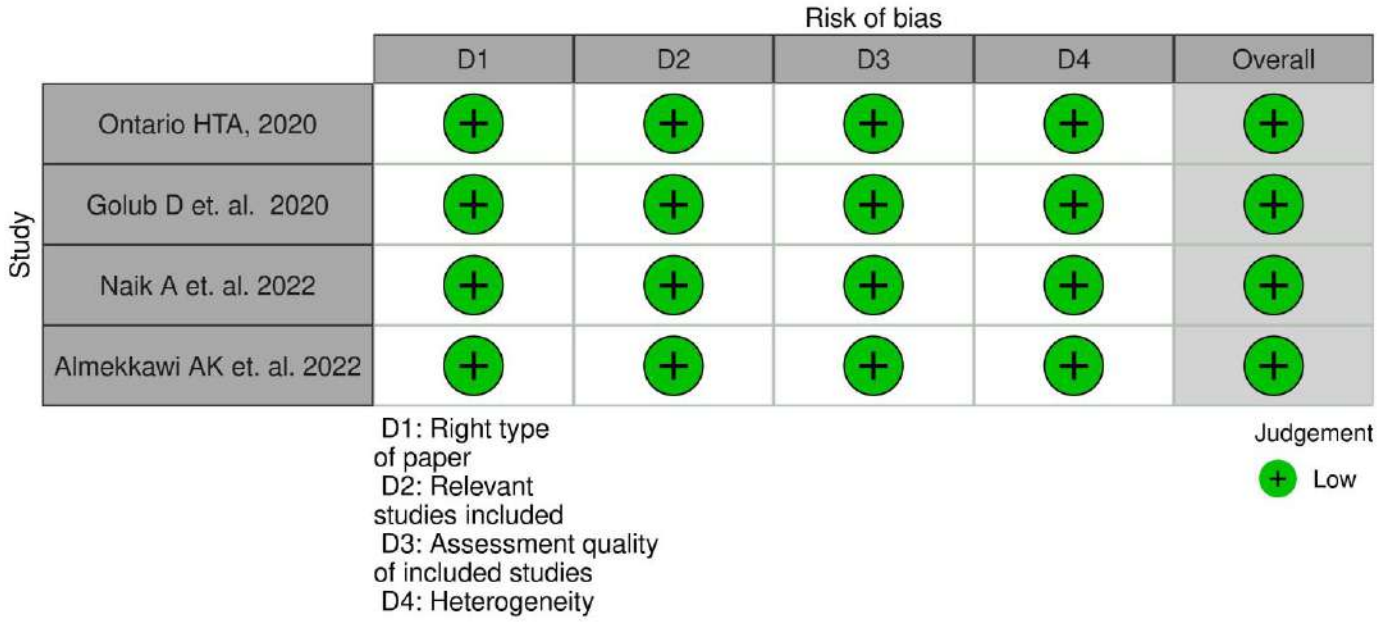

Figure 3.1: Risk of Bias of Systematic Reviews

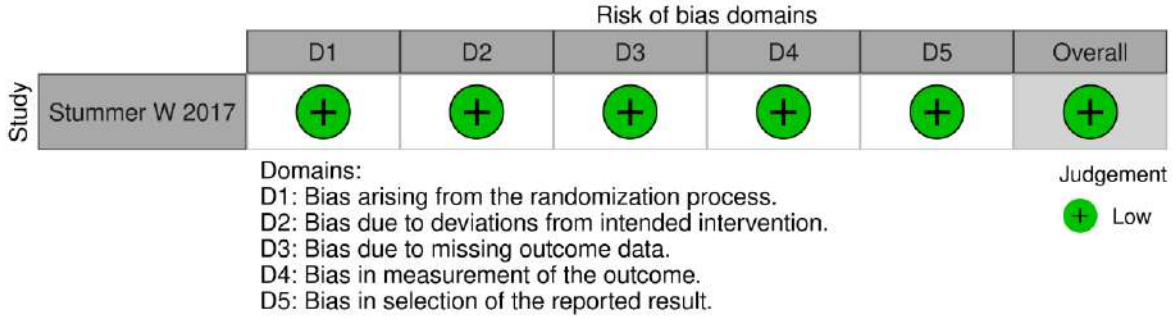

Figure 3.2: Risk of Bias of Randomised Control Trial

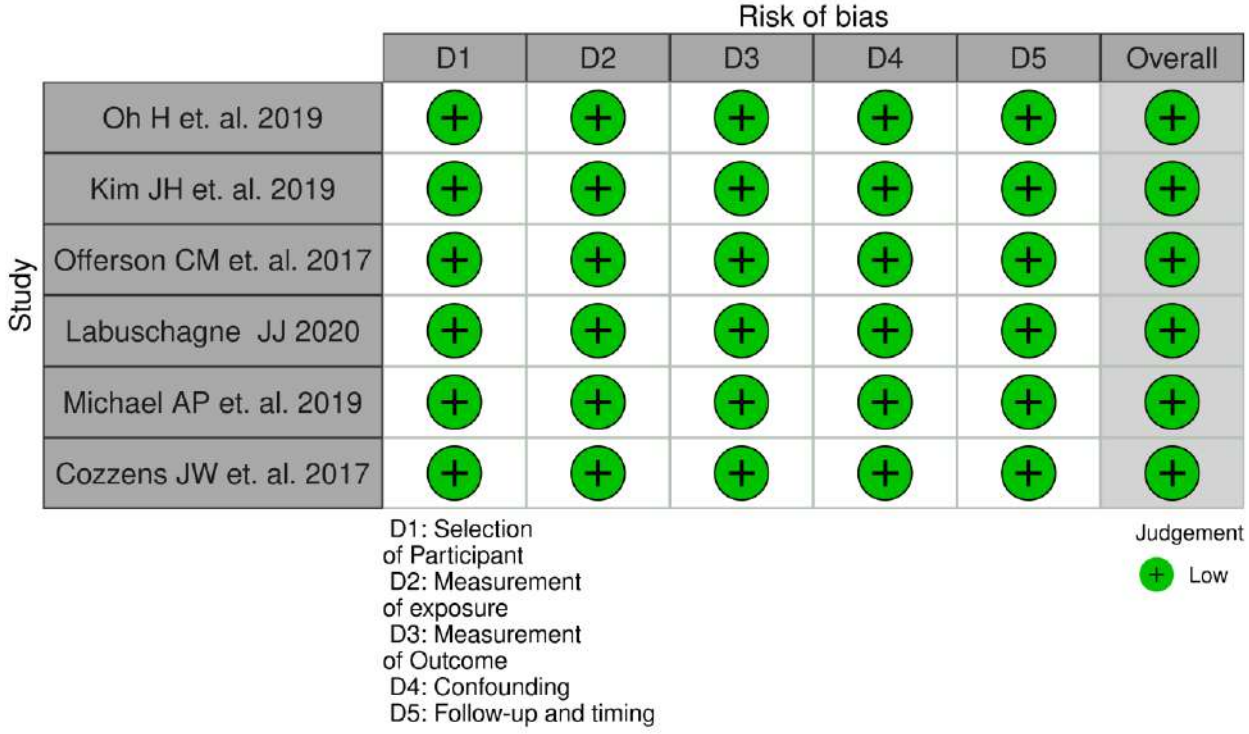

Figure 3.3: Risk of Bias on Cohort Study

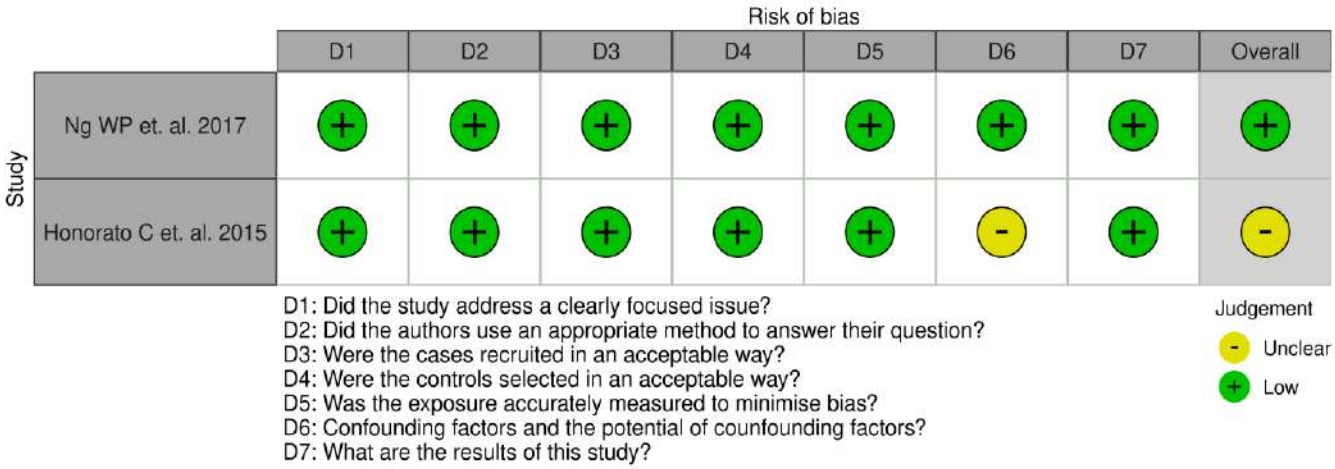

Figure: 3.5 Risk of Bias of Case-Control Study

5.1 EFFICACY / EFFECTIVENESS

Ontario Health (Quality) recently published a Health Technology Assessment (HTA) report on 5-ALA as a guide during high-grade gliomas (HGGs) surgery resection compared with standard care. The HTA evaluated the effectiveness, safety, budget impact of public funding 5-ALA, as well as patient preferences and values. Although 10 SR was selected, only one SR published in 2018 were included in final analysis of the HTA. Those nine reviews were excluded in the final analysis because these studies either did not report results quantitatively, or did not clearly defined the subgroup. Another reason was due to high risk of bias as well as outdated literature search. For the included SR, the study reported on one RCT with a total number of 322 newly diagnosed patients and untreated malignant gliomas which were eligible for complete resection. These patients were grouped into 5-ALA-guided surgical resection and standard intra-operative imaging technologies (white-light microscopy and neuro-navigation). Compared between both groups, complete tumour resection was increased in 5-ALA-guided group compared to standard care group. The increased was from 35% in standard care to 65% in 5-ALA-guided group. The finding corresponded to a relative risk [RR] of incomplete resection of 0.55 (95% CI 0.42 - 0.71) which favoured 5-ALA-guided resection. The GRADE for this body evidence was assessed by the review authors as low and the evidence was downgraded two levels due to multiple issues related to the risk of bias assessment. As for overall survival, the included SR reported no clear difference in overall survival either with 5-ALA or standard care; the hazard ratio for death was 0.82, 95% CI 0.62 - 1.07). For this findings, the authors of the HTA assessed the GRADE as low due to several limitations related to risk of bias. As for progression-free survival, the authors of the HTA extracted and analysed data directly from the RCT, they found that there was an improvement of 6-months progression-free survival for patients assigned 5-ALA in comparison to white-light microscopy group (41% [95% CI 32.8-89.2] versus 21.1% [95% CI 14.0-28.2] respectively; p = 0.003.[5, level 1]

Golub D et. al. conducted an SR and network meta-analysis (NMA) to evaluate the comparative effectiveness of 5-ALA and iMRI in optimizing the extension of resection (EOR) in HGGs. Eleven studies were included, those studies either described on the used of 5-ALA (in six studies) or iMRI (in seven studies). Both observational and interventional studies were included however, only articles that described at least one comparator group were included for analysis. During preliminary search, the authors revealed that there was a shortage of comparative prospective studies and RCTs on intra-operative navigational adjuncts which might limit their analysis. The most recent search of this SR was on January 25, 2019. In direct meta-analysis, both iMRI and 5-ALA were superior to conventional navigation in achieving gross-total resection (GTR); (OR 4.99, 95% CI 2.65–9.39, p < 0.001) and (OR 2.866, 95% CI 2.127–3.863, p < 0.001), respectively. As for survival, iMRI in comparison to conventional navigation prolonged both progression-free survival (standard differences in means [SDM] 0.656, 95% CI 0.330-0.983, p < 0.001) and overall survival (SDM 0.49, 95% CI 0.212-0.771, p = 0.001). Meanwhile for 5-ALA, the included studies showed that 5-ALA

improved both progression-free survival (SDM 0.495, 95% CI 0.068-0.922, p = 0.023) and overall survival (SDM 0.245, 95% CI 0.010-0.480, p = 0.041). Based on these individual studies, a network meta-analysis between iMRI and 5-ALA was performed. In order to compare the GTR rates between iMRI and 5-ALA, the authors assumed that the control group used conventional stereotactic navigation under white light. Based on Bayesian network analysis, neither intervention was found to be superior than GTR in HGG surgery; (OR 1.9, 95% CI 0.905, 3.989, p = 0.090).[13, level 1]

Another SR and NMA was conducted by Naik A et. al. in 2022. The study differed from previous NMA because, instead of comparing between 5-ALA and iMRI, the study also included another fluorescence guide substance which was fluorescein sodium (FS). The systematic search was conducted on August 23, 2021 and included observational multi-cohort studies and RCT published between 1997 and 2021. The primary outcome was GTR rate. The SR and NMA included 23 articles with a total number of 2,643 patients. Based on the included studies, the GTR rate in the iMRI, 5-ALA and FS were significantly superior to control (iMRI: 4.70 [95% CI 2.98 – 7.41]; p<0.01, 5-ALA: 3.41 [95% CI 2.58 – 4.51]; p<0.01 and FS: 4.06 [95% CI 2.90 – 5.69]; p < 0.01). However, with NMA estimation, there was no significant differences were observed among 5-ALA, iMRI and FS. An indirect comparison of FS and iMRI showed not significant result 0.86 (95% CI 0.45 – 1.52); p = 0.45. Meanwhile between 5-ALA and iMRI, the result was 0.71 (95% CI 0.43 – 1.18). Pooled results of four studies showed no significant difference in overall survival between 5-ALA and iMRI with control; (-0.40 [95% CI -0.92 – 0.12 and 0.05 [95% CI -0.37 – 0.47]). Direct estimated between the used of 5-ALA with FS also showed no significant differences in the OS (0.32 [95% CI -0.10 – 0.75]). No significant differences were observed between 5-ALA, iMRI and FS for OS. A NMA of five studies demonstrated the superiority of iMRI to other modalities and the marginal improvement of 5-ALA over control. This network was dependent on indirect-only comparisons for the iMRI-5-ALA and iMRI-FS arms. The iMRI was found to significantly increase PFS compared to 5-ALA (SMD = 5.98 [95% CI 4.78 – 7.17], p < 0.001) and FS (SMD = 6.0 [95% CI 4.76 – 7.24], p<0.001). On the other hand, the PFS in 5-ALA was marginally improved (SMD = -0.47 [95% CI -0.84 - -0.10], p = 0.03). The authors conducted surface under the cumulative ranking curve (SUCRA) hierarchical ranking to rank the optimal approaches in descending order.[14] The SUCRA is a numeric presentation of the overall ranking and presents a single number associated with each treatment. The SUCRA values range from 0 to 100%; the higher the SUCRA value, and the closer to 100%, the higher the likelihood that a therapy is in the top rank or one of the top ranks; the closer to 0 the SUCRA value, the more likely that a therapy is in the bottom rank, or one of the bottom ranks.[15] Thus, in the study by Naik et. al., to achieve maximal GTR, iMRI was ranked first (S = 0.869), followed by FS (S = 0.710) and 5-ALA (S = 0.421). As for maximal OS, the FS had the highest rank (S = 0.710), followed by 5-ALA (S=0.635). As for control and iMRI, the rank was lower (S=0.227, S=0.175, respectively). As for PFS, the iMRI was ranked first (s=1.0) with 5-ALA and FS ranked next (S=0.51, S=0.473, respectively. The control was ranked last with S=0.0163. Although all three intra-operative guidance significantly increased GTR rates when

compared to resection without any intra-operative guide, from the NMA, difference in GTR rates between those three were not statistically significant.[14, level 1]

Almekkawi AK et. al. conducted an SR to evaluate the current status of fluorescence-guided surgery (FGS) in low-grade glioma (LGG) and to assess the positive fluorescence rates and extent of resection (EOR). Twelve studies were included in the SR with a total number of 913 patients either with HGG or LGG. The LGG was histologically confirmed in 244 patients [26.7%]. All patients were treated between 2004 and 2016 and underwent FGS with 5-ALA. Overall, the included studies reported that the FGS with 5-ALA was successful to fluoresce in various types of brain tumours. One study reported the fluorescence was shown in 96% WHO grade IV gliomas, 83% of anaplastic oligoendrogliomas, 82% WHO grade III oligoastrocytomas, 42% WHO grade II astrocytoma, 33% grade II oligoastrocytomas and 100% grade II oligodendrogliomas. However, no resection rates or followed-up outcome was reported. Meanwhile, in another study the FGS was positive in 89.9% WHO grade III gliomas with total resection in 82% patients but the total resection rate was not stratified based on pathology. The study also reported that patient with WHO grade II gliomas did not demonstrate intra-operative fluorescence. Almekkawi AK et. al. also reported on categorization of 5-ALA fluorescence where the included studies categorised the positive fluorescence into none, weak, medium and strong fluorescence. One study reported that the extent of fluorescence was directly correlated with necrotic foci on pathology ($p = 0.026$). The same study reported that regardless type of glioma (either LGG or HGG), a total resection was found in 56.25% of patients, more than 95% resection in 12.5% of patients and more than 90% resection in 31.25% of patients. None EOR for LGG alone was reported. According to the study, the overall EOR was correlated with the duration between 5-ALA administration and surgical resection ($p = 0.038$). The SR also assessed correlation of 5-ALA with imaging techniques (MRI contrast enhancement and uptake ratio of 18F-fluoroethyltyrosine (FET)-position emission tomography) and glioma grading. Three studies included patients with various grades of gliomas and assessed the correlation of different modalities of imaging with fluorescence and glioma grading. The results for correlation of fluorescence with imaging techniques were summarised in Table 1. The overall finding showed that the fluorescence benefits more in HGG than LGG. It seems that 5-ALA fluorescence had low correlation with LGG and iMRI and confocal microscopy were helpful in negative fluorescence LGG.[16, level 1]

Table 1: Summary of correlation of 5-ALA with Imaging Techniques and Glioma

Studies	Observations	LGG	HGG
Study 1 N = 30 n = 13 LGG n = 17 HGG	Positive FET-uptakes / positive fluorescence combination	7.7% (n = 1/13)	70.6% (n = 12/17)
	Positive FET-uptake / Negative fluorescence combination	46.2% (n = 6/13)	17.6% (n = 3/17)
	Negative fluorescence / Negative FET uptake and Negative-contrast enhancement	46.2% (n = 6/13)	NA
Study 2 N = 33 n = 12 LGG n = 21 HGG	Fluorescence and iMRI	100% (n = 12) not fluoresce	100% positively fluoresce (n = 21)
		With iMRI / negative fluorescence LGG: Mean EOR = 89.2% versus Without iMRI / negative fluorescence LGG: Mean EOR = 68.7% (P = 0.098)	With iMRI / positive fluorescence HGG: Mean EOR = 92.6% versus Without iMRI / positive fluorescence HGG: EOR = 91.8% (P = 0.847)
Study 3 N = 10 LGG	Used both conventional and confocal microscopy visualization for 5- ALA at 3 points: i. Initial encounter of the tumour ii. Midpoint of tumour resection iii. Along brain-tumour interface	• None of the tumour showed visual positive fluorescence under standard SOP • Under confocal microscopy, all tumour positively fluoresces at point (i) and (ii) • At point (iii), fluorescence only seen in 60% of cases, median EOR (range 97% - 100%) and median residual volume 0.6cm^3 (range 0 – 2.6cm^3)	(not related)

Ng WP. et. al. conducted a case-control study to evaluate the overall survival and functional outcome of fluorescent-guided tumour resection in HGGs patients compared to those who underwent conventional surgery. This study also identified the significant predictors of survival among HGGs patients. The study involved 74 newly diagnosed HGGs who underwent surgical excision in the Neurosurgical Department of Hospital Sungai Buloh from January 2008 to December 2014. Out of 74 patients; 37 patients had fluorescent-guided surgical treatments (FG group; used 5-ALA) while another 37 patients underwent conventional surgery (conventional group). From January 2008 until April 2010, all HGGs patients were surgically treated using conventional white light method. However, since May 2010, the fluorescent-guided tumour resection with 5-ALA was utilised as the main surgical treatment for most of the HGGs in the centre, although some cases are still treated using conventional method. The decision regarding which surgical method to use was determined by the same senior consultant who performed the surgery, depending on the availability of 5-ALA at the time of surgery. There were no statistical differences in characteristics of the tumours based on functional location, laterality and primary site between the two groups.

Grade 4 gliomas were the most commonly diagnosed with a mean pre-operative tumour volume of 55.8cm^3 for the FG group and 53.0cm^3 for the conventional group. The records of progress made during each clinic visit from 1 January 2008 until 30 June 2015 were studied. Questionnaires were used to document all necessary details for each patient. Significant longer survival time (months) was observed in the FG group compared with the conventional group as the median length of survival from the time of surgery was 12 months (95% CI 10.1-13.8) in FG group and eight months (95% CI 5.1-10.9) in conventional group. Meanwhile, the survival rates for patients in FG group were 91.9% at 6 months, 42.8% at 12 months and 9.0% at 24 months and in conventional group 56.8%, 23.0% and 6.6%, respectively. Subgroup analysis was also performed, patients with pre-operative KPS 70-80 that underwent FG surgery had significant difference of longer median survival time (12 months 95% CI 9.5-14.5) compared to conventional group (7.0 months 95% CI 5.3-8.7), P = 0.008. Another subgroup was without adjuvant therapy, the HGG patients from FG group survived longer than those from the conventional group (8 months [95% CI 2.1 – 13.8] versus 3 months [95% CI 1.5 – 4.5], P = 0.006). The survival rate was significantly higher in FG group than conventional group; 44.4% versus 0% at six months, p = 0.006. Referring to Karnofsky Performance Scale (KPS) assessment after surgery, the mean post-operative KPS at six weeks for both groups were 82.4 (SD = 15.7) in FG group and 81.6 (SD = 15.7) in conventional group. At six months post-operatively, the KPS was significantly higher in the FG group (73.6) compared to conventional group (67.0), P = 0.024. However, there was no significant differences in post-operative KPS between the groups at 6 weeks and 6 months after surgery compared to pre-operative KPS; P > 0.995 and P = 0.832, respectively.[6, level II-2]

Labuschagne JJ et. al. conducted cross-sectional study to assess the experience regarding the safety and usefulness of FGS with 5-ALA for the resection of posterior fossa tumour (specifically ependymomas and medullablastoma) in children. Nineteen patients at mean age of five years old involved in the study. These patients were diagnosed with posterior fossa brain tumour and underwent brain tumour resection with FGS between January 2018 and October 2019. Single dose of 5-ALA 20 mg/kg of body weight was given orally to the patients four hour prior to the predicted surgery. The pathological diagnosis determined the tumour types based on WHO classifications which were ependymoma grade II in six patients, ependymoma grade III in four patients and MB grade IV in nine patients. In the MB group the 5-ALA was strongly fluorescing in 45% (n=4) of patients and another 55% (n=5) had combined heterogeneous or no fluorescence rate. In the ependymoma grade II group, 83% (n=5) of strong fluorescence rate, 17% (n=1) heterogeneous fluorescence rate and no patients with completely negative fluorescence were observed. Meanwhile in the ependymoma grade III group, 100% (n=4) strong fluorescence rate were observed. However, regardless the type of tumours, strong fluorescence rate was detected in 68% of patients (n = 13), 26% (n = 5 patients) had heterogeneous florescence rate and 5% (n = 1 patient) had completely negative fluorescence rate. No statistical relationship between tumour type and fluorescence was found (P = 0.163) when ependymoma groups were classified separately according to WHO grade. If ependymoma subtypes were combined,

strong fluorescence rate; 90%, was observed in ependymoma compared to 45% strong fluorescence rate in medullablastoma group and the difference was statistically significant (p = 0.05) for tumour subtypes and fluorescence rate. As for degree of resection, the authors attained post-operative MRI and confirmed a gross-total resection (GTR) in 73% of all tumours and another 17% was near-total resection. From the observation, the authors reported that the 5-ALA fluorescence was useful in 63% of cases and non-useful in 36% of cases. However, relationship between fluorescence and GTR as well as relationship between usefulness and resection was not significant; p = 1.00 and p = 0.603 respectively. At the end of the study, no patients had solid fluorescent tissue that still visible in surgical field.[17, level II-3]

Michael AP et. al. conducted a study to investigate residual tumour volume (RTV) at different 5-ALA doses. The study included 29 patients who were part of participants of prospective phase I and II clinical trial of 5-ALA for FGS. Out of 29 patients, four patients were excluded because their glioblastoma diagnosis was not confirmed histologically. The other 25 patients were all with WHO grade IV glioma and underwent first time resection with 5-ALA FGS. Those 25 patients were stratified into low and high dose group with five specific 5-ALA dose; low dose group (10 mg/kg in one patient [4%], 20 mg/kg in three patients [12%] and 30 mg/kg in two patients [8%]) and high dose group (40 mg/kg in 15 patients [60%] and 50 mg/kg in four patients [16%]). The volumetric analysis found that, median RTV for low dose group was 0.69 cm^3 compared to 0.00 cm^3 in high dose group, however, the difference was not significant; p = 0.975. The author also looked at the EOR, where the median EOR for low dose group was 98% compared to 100% in high dose group and the difference was also not significant; p = 0.883. Although the five dose-escalation groups were independently analysed, the results were remained not significantly correlated with RTV (P = 0.988) or EOR (P = 0.883). The observation also reported on GTR where the GTR in low dose group was achieved in 66.7% compared to 73.7% in high dose group, however the difference was not significant; p = 1.000. The complete resection of enhancing tumour (CRET) also not statistically significant (p = 0.180) between low dose and high dose group although higher in high dose group than low dose group; 52.6% vs 16.7%. For secondary outcome, a median OS for all patients was 16.4 months. In two years, the proportion of all patients alive at six, nine, 12 and 24 months was 84%, 76%, 60% and 16% respectively. Although OS of individual in low dose group and high dose group showed a slight difference, the difference was not statistically significant; P = 0.975. Another insignificant difference between low dose and high dose group was a volume of resection cavity. Although the average resection cavity volume was slightly higher in the low dose (87.2cm^3) compared to the high dose group (83.0cm^3), P = 0.929.[18, level II-1]

Stummer W et. al. conducted an RCT to detect dose-efficacy relationship between drug dose and overall tumour fluorescence. Twenty-one patients at aged between 18 and 75 involved in the study. The dose of 5-ALA studied were 20 mg/kg as a standard dose and low doses were 0.2 mg/kg and 2 mg/kg. All the 21 randomised patients underwent tumour resection and completed the 28 days followed-up. According to the primary objective, macroscopic

fluorescence in tumour core was highest in 20 mg/kg group and the surgeon estimated the entire viable tumour core to fluoresce in all cases. Meanwhile in 2 mg/kg group, generally the fluorescence was weak and not the entire tumour core fluoresces, even no fluorescence reported in one case. For the 0.2 mg/kg group, there was no fluorescence and was indicated as monotone, non-falling dose-efficiency relationship ($P < 0.0001$). This observation indicated that all groups differed significantly with respect to fluorescence quality and the extent of fluorescence with 20 mg/kg was the most effective within the tumour core. The finding was similar with results of fluorescence spectrographically. The authors also assessed the fluorescence intensity where the fluorescence intensity (strong, weak or none) were correlated significantly with spectrometrically determined fluorescence. Strong fluorescence was mostly perceived in the tumour core as identified under white light, whereas weak fluorescence was mostly found at the tumour margin. Ratio between tumour core or marginal tumour and normal adjacent brain was also determined. They found that ratio between regions with weak and strong fluorescence and normal brain were highest in group 20 mg/kg. Other findings reported in the study was significant positive correlation ($p = 0.011$) between tumour cellularity and spectrometrically determined fluorescence intensity was observed for 20 mg/kg only. The study also examined the pharmacokinetics of 5-ALA, the 5-ALA was rapidly absorbed after oral administration with t_{max} geometric mean values of 0.50-hour for 0.2/kg, 0.61-hour for 2mg/kg and 0.94-hour for 20mg/kg. The 5-ALA was quickly eliminated with a terminal half-life between 0.85 and 3.05-hour. The authors also observed the increment of plasma levels of PPIX after 2- and 20 mg/kg but not with 0.2mg/kg.[19, level II-1]

5.2 SAFETY

The U.S. Food and Drug Administration (FDA) approved 5-ALA (Gleolan®; photonamic GmbH & Co. KG) for used as an intraoperative optical imaging agent in patients with suspected HGGs in 2017. The European Medicine's Agency (EMA) had approved the 5-ALA as surgical adjunct of tumours resection in HGGs since 2007.[20]

Cozzens JW et. al. conducted a study to determine whether or not there were any dose-limiting toxicity (DLT) or harms at the doses studied. The study involved 19 patients aged between 27 and 88 who were diagnosed with high grade primary brain tumour and was indicated for surgery. The five 5-ALA doses studied were; 10 mg/kg, 20 mg/kg, 30 mg/kg, 40 mg/kg and 50 mg/kg. The DLT was determined by adverse events (AEs) and the AEs was graded following Cancer Therapy Evaluation Program of NCI Guidelines: AEs Reporting Requirements of January 1, 2005 and Common Toxicity Criteria/Common Terminology Criteria for AEs, skin reactions, serum AST and ALT elevations and nausea. One patient in 10 mg/kg group had delayed post-operative intracerebral haemorrhage resulted in death. Another patient experienced bone flap infection that require removal of bone flap on post-operative day 38. In 20 mg/kg group, one patient experienced minor wound dehiscence that required washout and re-closure on post-operative day 41 and another patient had fatal myocardial infarction on post-operative day 30. In 40 mg/kg group, one patient had

intracerebral haemorrhage in tumour resection cavity which was treated with observation only. Although several serious AEs occurred, the investigators and Data Safety Monitoring Board (DSMB) concluded that those AEs were not related to the 5-ALA. Two deaths occurred, the patients were at age of 74 and 75 years whom had significant pre-operative comorbidities and received low doses of 5-ALA. Meanwhile, patient with delayed wound complications also had significant comorbidities and underwent radiation therapy and received low dose of the study drug. No subject reported any nausea after the administration of oral 5-ALA. However, there were three instances of transient elevation of liver enzyme that resolved without treatment. These incidences were graded as grade 1 events and were not considered to be related to ingestion of the study drug. There was also one subjectively reported event on skin sensitivity to light by one patient who received the highest dose level of 5-ALA (50mg/kg). However, no family member or medical personal objectively confirmed the claim. Because of that, the investigators and the DSMB studied an additional three subjects at the 50mg/kg dose. Two out of those three patients reported skin redness and peeling but the medical providers were unable to confirm the observation. Thus the reports were considered by the DSMB as grade 1 AEs and not dose limiting.[21, level II-1]

Oh H et. al. conducted retrospective cohort study to evaluate the safety of 5-ALA in brain tumour patients with elevated pre-operative liver enzymes by investigating the incidence, severity and duration of post-operative increase in liver enzymes (PILE). The study involved 143 patients with increased of at least one pre-operative liver enzyme. These patients underwent brain tumour surgery with 5-ALA between September 2010 and February 2019 at Seoul National University Hospital (SNUH). Based on Common Terminology Criteria for Adverse Event (CTCAE), 97 episodes of PILE were observed in 61 patients (45.5%). The post-operative liver enzymes were increased in numbers of patients; serum alanine transaminase (ALT) increased in 41 patients (30.6%), aspartate transaminase (AST) in 33 patients (24.6%), serum alkaline phosphate in 6 patients (4.5%) and serum total bilirubin also increased in 17 patients (12.7%). Out of 143 patients, five (3.5%) and two (1.4%) of them showed grade 3 increased in ALT and AST, respectively. The maximum post-operative serum ALT and AST level were within range of 5.1 – 8.2 x ULN. The authors also monitored the period of the PILE incidences occurred, out of 97 PILEs, 11.3% incidences occurred at post-operative day (POD) of 0-1, 75.3% occurred at POD of 2–14 and 13.4% at POD of 15-30. They also conducted sub-group analysis to compare the maximum level of post-operative liver enzymes in pre-operative increase liver enzymes patients with those without pre-operative increase. The results were shown in Table 2. Overall, the maximal post-operative liver enzymes and total bilirubin were higher in patients with elevated pre-operatively. However, the incidence rates of increased post-operative ALT and AST based on CTAE were lower in patients with pre-operative increased in ALT and AST; 25.3% vs 45.7%, p = 0.024 and 10.3% vs 28.6%, P = 0.044, respectively. The PILE was temporary and resolved to baseline or normal level within POD 30. Out of 97 PILEs occurred; 80 PILEs (82.5%) was in grade 1, 10 PILEs (10.3%) was grade 2, and 7 PILEs (7.2%) was grade 3, then within POD 30 those PILEs were resolved to grade 2 (n=3 [3.1%]), grade 1 (n=24 [24.7%] or base line or normal (n=70 [72.2%]).[22, level II-2]

Table 2: Maximal post-operative liver enzymes and total bilirubin in patients with or without pre-operative increase in liver enzymes

Liver Enzymes and TB	Upper Limit of Normal (ULN)	Maximal post-operative liver enzymes		p-value
		With pre-operative increase liver enzyme	Without pre-operative increase liver enzyme	
ALT (U/L)	40.0	60.0 (42-101)	41.0 (21.0-64.0)	p < 0.001
AST (U/L)	40.0	42.0 (30.0-56.0)	29.0 (20.5-46.0)	p < 0.0011
ALP (U/L)	115.0	152.5 (116.5-196.5)	59.5 (50.0-74.0)	p < 0.001
TB (mg/dL)	1.2	1.1 (0.9-1.5)	0.8 (0.6-1.1)	p < 0.001

Kim JH et. al. also conducted retrospective cohort to determine whether pre-operative 5-ALA administration was associated with the development of post-operative elevation liver enzyme (PELE) in patients undergoing craniotomy for brain removal and to determine which factors were predictive on PELE in patients treated with 5-ALA. Electronic medical records of patients who underwent brain tumour surgery between January and December 2017 and who had preoperative liver enzymes levels within normal limits were reviewed. A total of 179 patients involved and 95 of them received 5-ALA. Out of 179 patients, 99 PELEs incidence were observed in 62 patients (34.6%). Post-operative elevation was detected in all three liver enzymes as well as total bilirubin; 56 patients in ALT, 34 patients in AST, 5 patients in ALP and 4 patients in TB. In patients with 5-ALA, three (3.2%), zero (0.0%) and one (1.1%) patient had ALT, AST and both criteria for grade 3 on CTCAE, respectively. However, the ALT and AST levels had returned to pre-operative baseline levels at POD 15-45. According to the multivariate analysis, a significant predictive factors for PELE in all patients were 5-ALA (OR 2.30 [95% CI 1.14 – 4.67] p = 0.021), pre-operative ALT level (OR 1.07 [95% CI 1.02-1.110], p = 0.002), BMI (OR 1.13 [95 CI 1.00-1.28]; p = 0.045) and mean blood pressure in ward (1.05 [1.00-1.10]; p = 0.033. On the other hand, multivariate analysis showed that significant predictive factors for PELE among 5-ALA-treated patients were pre-operative ALT level (OR 1.10 [95% CI 1.04-1.17]; P = 0.001) and BMI (OR 1.29 [95% CI 1.08-1.56]; P = 0.006). Among 95 patients treated with 5-ALA, 41 patients (43.2%) showed 70 PELEs; 39 patients with elevated ALT, 22 patients with AST elevation, 5 patients with elevated ALP and 4 patients with elevated TB. Patients with PELE had a higher BMI, SBP and MBP in ward and pre-operative ALT level than those without PELE.[23, level II-2]

Offersen CM et. al. conducted retrospective cohort to assess the potential risk of liver damage and investigate liver enzyme reactions of patients going through 5-ALA-guided operations to improve monitoring of the operation. Ninety-nine patients from University Hospital of Copenhagen who underwent surgery with 5-ALA for suspected malignant glioma from 1 September 2012 until 30 September 2014 were included in the study. Their liver function was evaluated with enzymes ALT, AST, GGT and amylase both prior to 5-ALA-guided surgery and on day 1, 7 and 14. All measurements were taken before chemotherapeutic treatment. A total number of 119 surgeries were conducted on 99, of which 93% had glioblastoma WHO grade IV. From the records, a total of 50 cases (42% of 119 operations) had at least one or multiple elevations of post-operative enzyme levels; ALT (26%), AST (12%), GGT (13%) and amylase (13%). After surgeries there were no jaundice or other symptoms suggestive of liver injury such as itching and abdominal discomfort reported except one case of skin rash following accidental exposure to light after post-administration of 5-ALA. None of the patients had enzymes elevation more than three times ULN was observed. The developments of the enzyme levels were followed-up for a maximum of 30 days and the authors reported that post-surgical time of surveillance was not equivalent in all

four enzymes and after day one, a decreasing number of available samples was observed.[24, level II-2]

Honorato C. et. al. conducted a case-control study focusing on the most two factors that affect anaesthetic practice; light protection protocol throughout the operative process and risks of anaemia and thrombocytopaenia. The patients involved were 260 patients who underwent brain surgery between 2008 and 2015. The brain surgery either with 5-ALA (5-ALA group: 207 patients) or without 5-ALA (Non-5-ALA group: 53 patients). Overall, patient's characteristics were similar in both group, except a higher American Society Score of Anaesthesia Risk Score (ASA) and tumour grades in 5-ALA group than non-5-ALA group; 80.7% grade IV versus 18.9%. Haemoglobin, platelet and white cell levels were tested preoperatively, immediately after surgery, at 24-hour and at 7- to 10-day follow-up. Any variation more than 20% from previous values were considered clinically relevant. Any skin lesion including erythema, blister or ulcers occurred after 5-ALA administration was observed as a skin reaction. Fortunately, no skin reaction was reported in any 207 patients in 5-ALA group. Blood counts in both groups showed no significant difference either in any haemoglobin or platelet level throughout the study. However, when looking at haemoglobin and platelet trends regarding intervention number, tumour grade or surgical duration, only surgical duration showed a statistically significant correlation in the 5-ALA group. In post-operative MRI, patients in the 5-ALA group showed significant lower percentage of residual bleeding than non-5ALA group (19% of all patients; 17.9% in 5-ALA group and 22.7% in non-5-ALA group; $p = 0.04$). Other findings reported were, eight patients in the 5-ALA group required blood transfusion (3.9%) compared with two patients in the non-5 ALA group (3.8%). Due to reported bleeding, four patients in 5-ALA group required re-intervention in the first 48-hours. However, none of the incidence had platelets less than 150,000/mL. Although one death was reported in 5-ALA group, the fatality was not related to 5-ALA administration as it was linked to intracerebral haemorrhage secondary to hypertensive crisis.[25, level II-2]

The HTA by Ontario Health (Quality) reported that the adverse events between 5-ALA and standard care groups was insufficiently reported. The included SR could not calculate the relative risk and the association between events and intervention. Besides, no information regarding the timing of events or number of individuals with more than one event were available. Overall the SR reported that number of participants with a deterioration in the National Institutes of Health Stroke Scale compared to baseline was higher in 5-ALA group at 48 hours (26.2% with 5-ALA versus 14.5% in control group) but not at seven days (20.5% versus 10.7%), six weeks (17.1% versus 11.3%) and three months (19.6% versus 18.6%).[5, level 1]

Labuschagne JJ et. al. in their cross-sectional study reported that three out of 19 patients developed complications. First patient developed transient cranial nerve IV palsy from cerebrospinal fluid over drainage, and developed left-sided central nerve VI palsy that resolved rapidly after clamping and drain removal. Second patient developed cerebellar mutism and emotional ability which was the characteristics of posterior fossa syndrome that partially resolved during last clinical visit. Third patient had worsening of ataxia that recovered within six weeks. All the complications were confirmed not directly related to the administration of 5-ALA.[17, level II-3]

5.3 ORGANISATIONAL ISSUES

5-ALA requires a surgical microscope connected to a xenon light source that can emit 370–440 nm wavelength light to excite PpIX and the use of a filter to visualize the red tumor fluorescence with emission peaks at 635–704 nm). [14, level 1]

5.4 SOCIAL ISSUES

The Ontario Health (Quality) HTA also analysed patient's preferences and values. The purpose of the analysis was to explore the underlying preferences, value, needs and priorities of those who have lived experienced with high-grade glioma. The engagement plan of the HTA focused on consultation to examine the experiences of people with HGG, the families and other caregiver. The engagement was via a telephone interview and followed-up through email. The authors applied purposive sampling approach that actively reached-out people with direct experience of the health condition and health technology or intervention review. The interview lasted about 30 minutes and consisted of loose structured and series of open-ended questions. The questions focused on the impact of HGG n the person's quality of life, their experiences with treatments to manage or treat the condition, their experiences with 5-ALA-guided resection and their perceptions of the benefits or limitation of 5-ALA in glioma resection. The summary of the analysis was simplified in Table 3. Overall, the patients expressed their greater satisfaction with 5-ALA-guided resection compared to standard surgical resection.[5, level 1]

Table 3: Patient Preferences and Values

Domains	Patients Preferences and Values (Reported by the Participants)
Diagnosis of Glioma (the symptoms)	• Did not experience any obvious symptom at first • Physical changes in head area required further investigation including biopsy
Impact from the diagnosis result	• Family members and friends: in shock • Participant: not much change in day-to-day life although poor prognosis
Treatment with standard surgical resection	• Participant: get standard treatment before eligible for 5-ALA-guided surgery and for the standard treatment they could see the surgeon work. • The surgeon left everything they could see and some part of the tumour were left behind to avoid any sensory damage
Diagnosis of high-grade glioma	• On regular follow-up scans, another mass in the same spot were detected and was progressed to Grade III or IV glioma • 2nd surgery was eligible for 5-ALA-guided
Treatment with 5-ALA guided resection	• Taste of oral -5ALA: bitter taste • Had strange sensation on teeth for a few minutes • The participant felt that 5-ALA-guided procedure provided more accurate results • Main risked being discussed with them: potential sensitivity to light and was advised to not directly look on the phone for a long period

5.5 COST-EFFECTIVENESS

The price of 5-ALA is about RM9,000 to RM10,000 per vial and each surgery require for 1 vial of 5-ALA.

The HTA by Ontario Health (Quality) reported five cost-utility analyses studies were identified from economic literature search. These studies met the inclusion criteria as the studies evaluated the of 5-ALA–guided surgical resection for HGG compared to standard white-light operating microscope ("white-light microscopy"). Most of these studies found that 5-ALA–guided surgical resection was cost-effective as compared to white-light microscopy for HGGs. However, all studies derived clinical model inputs of the comparative safety and effectiveness parameters of 5-ALA from limited and low-quality evidence. Public funding of 5-ALA–guided surgical resection in Ontario over the next 5 years would result in a budget impact of about $930,000 in year 1 to about $1,765,000 in year 5, yielding a total budget impact of about $7,500,000 over this period.[5, level II-1]

Warsi NM et. al. conducted an SR to analyse the state of evidence pertaining to health economic studies on 5-ALA-guided HGG surgery. The SR included full-text health-economic analyses reporting on health economics or cost-effectiveness of 5-ALA HGG or glioblastoma and the evidences were synthesized and evaluated in terms of validity of assumptions and generalizability across health care models and systems. Three primary studies were included, and were conducted in European nations; Portugal, Spain and France. First study which was published in 2015 evaluated the cost-effectiveness (CE) of 5-ALA-induced fluorescence in malignant glioma surgery in Spain. The study assessed the cost-utility of 5-ALA in terms of incremental costs per quality adjusted life-years (QALY) gained. The data was derived from another retrospective observational study (VISIONA) and compared the effectiveness of the 5-ALA with white light surgery. To calculate the QALY, the authors assessed the clinical impact of the surgery used complete resection rate and progression free survival (PFS). The difference in QALY between 5-ALA and white-light surgery was defined as an increase in PFS following adjuvant treatment multiplied by utility factor. The incremental cost was paid at time of surgery and no modelling or discounting were applied in the study. The incremental cost per surgery, complete resection and QALY gained between 5-ALA and white-light cohorts were calculated. For PFS, the authors found statistically significant difference in six-months PFS between 5-ALA and white-light cohorts (69% versus 48%; p = 0.02) but the cost difference per PFS were not evaluated. The higher proportion of complete resection was seen in 5-ALA cohort than without 5-ALA; 67% versus 45%; p = 0.001). The economic results were shown in Table 4. Another included study was also published in 2015 and was conducted in Portugal. The study also compared 5-ALA-guided surgery and white-light surgery. The Markov model was developed to simulate a natural history disease, deterioration of clinical condition and subsequent fluctuations in health related quality of life (HRQoL) that involved five health states. The probabilistic results were summarised in Table 2. Another study was conducted in France. The study was evaluated

the current trend in the management of glioblastoma multiforme (GBM) in French University Hospital and the associated direct cost. The study provided report of cost and changes in GBM management within the three years including introduction of 5-ALA guided resection in 2008. No modelling and discounting applied. The results of the study were reported in Table 4. All three studies were rated as average to moderate, however, study from Portugal was the strongest evidence as it involved largest number of guideline parameters. Referring to the results in Table 4, it was suggested that the use of 5-ALA as an intraoperative adjunct may be cost-effective.[26]

Table 4: Summary of Cost-Effectiveness Study

	Studies		
	Spain (2015 Slof et. al.)	**Portugal (Pilot study) (2015 Esteves et. al)**	**France (2016 Henaine et. al.)**
ICER	€4,550/C$6,813 per complete resection in the 5-ALA group Subgroup analysis for average adapting 5-ALA equipment: Incremental cost per complete resection gained was €5,019/C$7,516	• ICER per QALY gained: €12,933 / C$19,367 (95% CI €8,283 / C$12,403 - €21,315 / C$31,918) • Mean ICER per PFLY: €9,841 / C$14,736 (95% CI: €5,025 / C$7,525 - €17,578 / C$26,322) • Mean ICER per LY: €7,386 / C$11,060 (95% CI €4,995 / C$7,480 - €12,631 / C$18,914) • The probability of 5-ALA being cost-effective at a €20,000 threshold was 96% based on QALY, 99.6% based on LY, and 98.8% based on PFLY ✓Discounting rates of 0%, 3%, 5% and 7% were applied with: • ICER per LY: gained ranging from €5,963 / C$8,885 to €7,473 / C$11,135 • ICER per QALY: gained ranging from €8,250 / C$12,293 to €10,127 / C$15,089 • ICER per PFLY: gained ranging from €8,174 / C$12,179 to €9,678 / C$14,420	
QALYs gain	0.11 in 5-ALA over white-light		
ICUR	€9,021/C$13,508 (acceptable cost-effectiveness threshold in Spain [€30,000-45,000]) Subgroup analysis for average adapting 5-ALA		

	Studies		
	Spain (2015 Slof et. al.)	**Portugal (Pilot study) (2015 Esteves et. al)**	**France (2016 Henaine et. al.)**
	equipment: ICUR: €9,950/C$14,900		
Direct cost			✓ Mean total cost of surgical stay: • €10,118 ± 5803 (C$15,936 ± 9,140 in 2004), • €8,421 ± 3,672 (C$13,264 ± 5,783 in 2008), • €9,353 ± 4,421 (C$14,732 ± 6,963 in 2011) ➔ When comparing the values across those 3 times period: no statistically significant differences
Sensitivity analysis	✓ Sensitivity analyses and recalculated cost-effectiveness used the least favourable variations of the parameters used initial calculations ✓ In least favourable scenario: • IC per CR gained: €9,695 / C$14,446 • IC per QALY: €19,222 / C$28,641 ➔ Detailed results of the robustness were not provided	✓One-way and probabilistic analyses: • Results were robust to uncertainties in model parameter as well as different discounting rates: 0%, 3%, 5% and 7% • Proportion of patients with CR in 5-ALA cohort and 2 transition probabilities from stable state with complete and partial resection to progressive disease were also evaluated with sensitivity analyses ✓ICER per QALY gained was below €14,000 / C$20,860 in all plausible variations of different willingness-to-pay thresholds with join parameter uncertainty ✓In all plausible willingness-to-pay thresholds tested: • ICER below €9,000 / C$13,410 per LY gained and ICER below €12,000 / C$17,880 per PFLY gained	None

5.4.1 Financial Implication

In Malaysia, the use of 5-aminolevulinic acid (5-ALA) as an intraoperative optical adjunct for high grade glioma (HGG) patients showed improved surgical resection, superior to conventional white light visualisation. To utilise 5-ALA as an optical imaging agent, it requires a neurosurgical microscope system with special module that enables 5-ALA induced fluorescence visualization. The one time oral 5-ALA is administered to the patient 2-4 hours prior to surgery. It is assumed that the staffing and post-operative treatment is similar in both 5-ALA cohort and conventional method. Hence, the calculation of costing of using 5-ALA is

an addition on top of the conventional white light visualisation. In neurosurgical centres without the neurosurgical microscope system, the additional cost taken includes the equipment investment and cost of 5-ALA.

Table 5: Cost parameters

Parameters
Optical visualizing agent (5-ALA)
Microscope capital expenditure (inclusive of 2 years maintenance service and warranty)
Microscope yearly maintenance (6.05% of acquisition cost, from year 3 onwards)

The financial implication is depicted in two types of neurosurgical centres (scenario A and scenario B), namely the neurosurgical centers with an existing microscope system to utilize 5-ALA; and the neurosurgical centers without the microscope system.

Scenario A: In neurosurgical centres with an existing microscope with fluorescence targeting 5-ALA module.

Assuming low patient load neurosurgical centre with minimum of 5 patients per year; high patient load neurosurgical center with maximum of 50 patients per year.

Table 6: Cost of 5-ALA

Year	Minimum cost (5 patients)	Maximum Cost (50 patients)
1	RM34,000.00	RM340,000.00
2	RM34,000.00	RM340,000.00
3	RM34,000.00	RM340,000.00
4	RM34,000.00	RM340,000.00
5	RM34,000.00	RM340,000.00
6	RM34,000.00	RM340,000.00
7	RM34,000.00	RM340,000.00
8	RM34,000.00	RM340,000.00
9	RM34,000.00	RM340,000.00
10	RM34,000.00	RM340,000.00
Total / year	**RM34,000.00**	**RM340,000.00**

Scenario B: In neurosurgical centres without existing microscope with fluorescence targeting 5-ALA module.

Assuming low patient load neurosurgical centre with minimum of 5 patients per year; high patient load neurosurgical center with maximum of 50 patients per year.

Table 7: Cost of 5-ALA with initial microscope system acquisition and subsequent maintenance (from year 3 onwards)

Year	Minimum cost (5 patients)	Maximum Cost (50 patients)
1	RM2,254,000.00	RM2,560,000.00
2	RM34,000.00	RM340,000.00
3	RM168,310.00	RM474,310.00
4	RM168,310.00	RM474,310.00
5	RM168,310.00	RM474,310.00
6	RM168,310.00	RM474,310.00
7	RM168,310.00	RM474,310.00
8	RM168,310.00	RM474,310.00
9	RM168,310.00	RM474,310.00
10	RM168,310.00	RM474,310.00
Total/ year	**RM363,448.00**	**RM669,448.00**

The average cost over 10 years is calculated. In neurosurgical centers that have existing suitable neurosurgical microscope system to use 5-ALA, the minimum additional cost is RM34,000.00 per year and the maximum cost is RM 340,000.00 per year. (Table 6) However, the cost is higher in neurosurgical centers without existing microscope system with fluorescence targeting 5-ALA module, the minimum cost is RM363,448.00 per year to a maximum cost of RM669,448.00 per year. (Table 7)

As for per patient, in the neurological centre with existing microscope system for 5-ALA, the additional cost of RM6,800 per patient per year is required. The cost per patient per is similar between minimal cost (A) and maximal cost (B) because the cost involved is only the cost of 5-ALA as the microscope cost and the maintenance coast already absorb with the patients cost all over the years. (Table 8)

Meanwhile, with newly setup microscope system for 5-ALA, the neurosurgical centre require additional cost of RM13,000 to RM72,000 as the microscope and the maintenance cost gradually absorb with the patients all over the years. (Table 8)

Table 8: Cost per patient per year

Scenario	A) Minimal cost (5 patients/year)	B) Maximal cost (50 patients/year)	Cost/1 patient/year
Scenario A	RM34,000	RM340,000	(A & B) RM6,800
Scenario B	RM363,448	RM669,448	A) RM72,689.60 B) RM13,388.96

5.6 LIMITATIONS

There were some limitations in the review and these should be considered when interpreting the results. The selection of the studies and appraisal was done by one reviewer. Besides, only English full text articles were included. There is also related full text articles could not retrieve because of database limitation.

6.0 CONCLUSION

Based on the review 5-ALA improved progression free survival (PFS), gross total resection (GTR) and overall survival (OS) as compared to conventional treatment or white light surgery in high grade glioma (HGG). However, when compared with iMRI and fluorescein sodium, the difference was not significant. There was no difference in the outcome measure with low- or high-dose of 5-ALA. Overall, the used of 5-ALA was safe although there were a few incidence of transient elevation of liver enzymes and skin sensitivity which later on resolved without further treatment. On the economic side, 5-ALA have a potential of cost-effective as compared to white-light microscopy for HGGs. As for financial implication, the neurosurgical centre with the existing microscope system for 5-ALA will incur additional cost of RM6,800 per patient per year. Meanwhile, the neurosurgical centre with newly set-up microscope system for 5-ALA will require the treatment cost per patient per year range from RM13 000 to RM72 000.

7.0 REFERENCES

1. https://www.cancer.gov/search/results?swKeyword=brain+tumor
2. https://medlineplus.gov/braintumors.html#summary
3. Othman AK, Udin N, Shab MS et. al. Demographic Study of Brain Tumour in a Neurosurgical Department in Terengganu, Malaysia. Med. J Malaysia. 2020; 75
4. Balqis N, Zahary MN, Hidayah N et. al. Distribution Pattern Of Brain Tumour In A Tertiary Hospital In East Coast, Malaysia. Malaysian Journal of Public Health Medicine 2017; (2): 41-48
5. Ontario Health (Quality). 5-Aminolevulinic acid hydrochloride (5-ALA)–guided surgical resection of high-grade gliomas: a health technology assessment. Ont Health Technol Assess Ser [Internet]. 2020 Mar;20(9): 1–92. Available from: https://hqontario.ca/Evidence-to-Improve-Care/Health-Technology-Assessment/Reviews-And-Recommendations/5-Aminolevulinic-Acid-Hydrochloride-5-ALA-Guided-Surgical-Resection-of-High-Grade-Gliomas
6. Ng WP, Liew BS, Idris Z, Rosman AK. Fluorescence-guided versus conventional surgical resection of high-grade glioma: a single-centre, 7-Year, comparative effectiveness study. Malays J Med Sci. 2017;24(2):78–86. https://doi.org/10.21315/mjms2017.24.2.10
7. Schupper AJ, Rao M, Mohammadi N et. al. Fluorescence-Guided Surgery: A Review on Timing and Use in Brain Tumour Surgery. Front Neurol. 2021; 12:682151. doi: 10.3389/fneur.2021.682151
8. Yamamoto J, Kitagawa T, Miyaoka R et. al. 5-Aminolevulinic Acid: Pitfalls of Fluorescence-guided Resection for Malignant Gliomas and Application for Malignant Glioma Therapy. J UOEH. 2020;42(1):27-34
9. Orillac C, Stummer W & Orringer DA. Fluorescence Guidance and Intraoperative Adjuvants to Maximize Extent of Resection. Neurosurgery. 2021; 89: 727-736
10. Fountain DM, Jenkinson MD, Bryant A, Vale L, Bulbeck H, Hart MG, Barone DG. Intraoperative imaging technology to maximise extent of resection for glioma: a network meta-analysis (Protocol). Cochrane Database of Systematic Reviews 2020, Issue 5. Art. No.: CD013630. DOI: 10.1002/14651858.CD013630.
11. Dadario NB, Khatri D, Reichman N et. al. 5-Aminolevulinic Acid – Shedding Light on Where to Focus. World Neurosurg. 2021; 150: 9-16
12. Widhalm G. 5-Aminolevulinic Acid (5-ALA) in Brain Tumour Surgery. Medical University of Vienna, 01/2013. (Thesis Paper)
13. Golub D, Hyde J, Dogra S et. al. Intraoperative MRI versus 5-ALA in High-Grade Glioma Resection: a Network Meta-Analysis. J Neurosurg. 2020. Doi:10.3171/2019.12JNS191203
14. Naik A, Smith EJ, Barreau A et. al. Comparison of fluorescein sodium, 5-ALA and intra-operative MRI for resection of high-grade gliomas: a systematic review and network meta-analysis. J Clin Neuroscience. 2020; 98: 240-247
15. Mbuagbaw L, Rochwerg B., Jaeschke R. et. al. Approaches to interpreting and choosing the best treatments in network meta-analyses. Systematic Reviews. 2017; 6: 79
16. Almekkawi AK, Ahmadieh TY, Abunimer AM, Abi-Aad K, Aoun SG, Plitt AR, El Tecle NE, Stummer W & Bendok BR. The Use of 5-Aminolevulinic Acid in Low-Grade Glioma Resection: A Systematic Review. Operative Neurosurgery. 2020; 19:1-8
17. Barone DG, Lawrie TA, Hart MG. Image guided surgery for the resection of brain tumours. Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD009685. DOI: 10.1002/14651858.CD009685.pub2.

18. Labuschagne JJ. The Use of 5-Aminolevulinic Acid to Assist Gross Total Resection of Paediatric Posterior Fossa Tumours. Pediatr Neurosurg. 2020; 55: 268-279 Doi: 10.1159/000511289
19. Stummer W, Stepp H, Wiestler OD & Pichlmeier U. Randomised, Prospective Double-Blinded Study Comparing 3 Different Doses of 5-Aminolevulinic Acid for Fluorescence-Guide Resections of Malignant Gliomas. Neurosurgery. 2017; 0:1-10
20. Hadjipayanis CG, Widhalm G & Stummer W. What is the Surgical Benefit of Utilizing 5-ALA for Fluorescence-Guided Surgery of Malignant Gliomas? Neurosurgery. 2015; 77(5): 663–673. doi:10.1227/NEU.0000000000000929.
21. Cozzens JW, Lokaitis BC, Moore BE, Amin DV, Espinosa JA, MacGregor M, Michael AP, & Jones BA. A Phase 1 Dose-Escalation Study of Oral 5-Aminolevulinic Acid in Adult Patients Undergoing Resection of a Newly Diagnosed or Recurrent High-Grade Glioma. Neurosurgery. 2017; 0: 1-10
22. Oh H, B. Park, H.K Yoon et al., Effects of Preoperative 5-aminolevuinic aid administration on postoperative liver enzymes after brain tumour surgery in patients with elevated preoperative liver enzymes, Journal of Clinical Neuroscience, https://doi.org/10.1016/j.jocn.2019.08.118
23. Kim JH, Yoon HK, Lee HC, Park HP, Park CK, Dho YS & Hwang JW. Preoperative 5-Aminolevulinic Acid Administration for Brain Tumour Surgery is Associated with an Increase in Postoperative Liver Enzymes: a Retrospective Cohort Study. Acta Neurochir (Wien). 2019 Nov;161(11):2289-2298. doi:10.1007/s00701-019-04053-6
24. Offersen CM & Skjoeth-Rasmussen J. Evaluation of the Risk of Liver Damage from the Use of 5-Aminolevulinic Acid for Intra-Operative Identification and Resection in Patients with Malignant Gliomas. Acta Neurochir (Wien). 2017; 145-150. Doi:10.1007/s00701-016-3014-y.
25. Honorato C, Martinez-Simon A, Cacho-Asenjo E, Guillen-Grima F, Tejada-Solis S & Diez-Valle R. Safety Profile of 5-Aminolevulinic Acid as a Surgical Adjunct in Clinical Practice: A Review of 207 Cases from 2008 to 2013. J Neurosurg Anethesiol. 2015; 27: 304-309
26. Warsi NM, Zewude R, Karmur B, Pirouzmand N, Hachem L, Mansouri A. The Cost-Effectiveness of 5-ALA in High-Grade Glioma Surgery: A Quality-Based Systematic Review. Can J Neurol Sci. 2020 Nov;47(6):793-799. doi: 10.1017/cjn.2020.78. Epub 2020 Apr 24. PMID: 32329422.
27. Jenkinson MD, Barone DG, Bryant A, Vale L, Bulbeck H, Lawrie TA, Hart MG, Watts C.Intraoperative imaging technology to maximise extent of resection for glioma. Cochrane Database of Systematic Reviews 2018, Issue 1. Art. No.: CD012788.

8.0 APPENDIX

APPENDIX 1: LITERATURE SEARCH STRATEGY

Database: Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations <1946 to January 07, 2022>

Search Strategy:

---

1 Astrocytoma/ or Glioblastoma/ or Brain Neoplasms/ or Glioma/
2 ((malignan$ or benign or primary) adj2 brain neoplasm$).tw.
3 (Brain adj2 (primary or malignan$ or benign) adj neoplasm$).tw.
4 (Brain adj2 cancer$).tw.
5 Brain malignan$ neoplasm$.tw.
6 Brain metastase$.tw.
7 (Brain adj3 neoplasm$).tw.
8 (Brain adj3 tumo#r$).tw.
9 (Brain adj3 tumo#r$ adj1 (primary or recurren$)).tw.
10 Intracranial neoplasm$.tw.
11 ((malignan$ or benign or primary) adj2 brain tumo#r$).tw.
12 (Glial cell$ adj1 tumo#rs).tw.
13 Glioma$.tw.
14 (Glioma$ adj1 malignan$).tw.
15 (Glioma$ adj mix$).tw.
16 (Astrocytoma adj2 grade iv).tw.
17 (Giant cell$ adj2 glioblastoma$).tw.
18 Glioblastoma$.tw.
19 (Glioblastoma$ adj1 multiforme).tw.
20 (Anaplastic adj2 astrocytoma$).tw.
21 (Astrocytic adj2 glioma$).tw.
22 Astrocytoma$.tw.
23 (Astrocytoma$ adj2 (cerebral or fibrillary or gemistocytic or grade i or grade ii or grade iii or intracranial or pilocytic or protoplasmic or anaplastic)).tw.
24 (Astrocytoma$ adj2 childhood cerebral).tw.
25 (Astrocytoma$ adj juvenile pilocytic).tw.
26 (pilocytic astrocytoma$ adj2 juvenile).tw.
27 (Astrocytoma$ adj2 subependymal giant cell$).tw.
28 Astroglioma$.tw.
29 Cerebral astrocytoma$ childhood.tw.
30 (mixed adj oligoastrocytoma$).tw.
31 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32 Aminolevulinic Acid/
33 (Aminol#evulinic adj acid$).tw.
34 (Aminol#evulin$ adj acid$).tw.
35 5 aminol#evulin$.tw.
36 5-aminol#evulin$.tw.
37 88755taz87.tw.
38 (Delta-aminol#evulin$ adj acid$).tw.
39 (Delta aminol#evulin$ adj acid$).tw.
40 (Aminol#evulin$ adj acid$ hydrochlori$).tw.
41 (Hydrochlori$ adj aminol#evulin$ acid$).tw.
42 L#evulan.tw.
43 v35kbm8jgr.tw.
44 5-ALA.tw. (1302)
45 5 ALA.tw. (1302)

Other Databases

EBM Reviews - Health Technology Assessment
EBM Reviews - Cochrane database of systematic reviews
EBM Reviews - Cochrane Central Registered of Controlled Trials
EBM Reviews - Database of Abstracts of Review of Effects
EBM Reviews - NHS economic evaluation database

} Same MeSH, keywords, limits used as per MEDLINE search

PubMed
INAHTA
US FDA

} Same MeSH and keywords as per MEDLINE search

APPENDIX 2: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS

DESIGNATION OF LEVELS OF EVIDENCE

I	Evidence obtained from at least one properly designed randomized controlled trial.
II-I	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 3: EVIDENCE TABLE

(Available upon request)

5- AMINOLEVULINIC ACID (5-ALA) FOR BRAIN TUMOUR SURGICAL PROCEDURE TECHNOLOGY REVIEW (TR)

Cawangan Penilaian Teknologi Kesihatan (MaHTAS)