

## Research Article

# Usefulness of Fluorescence-Guided-Surgery in Achieving Gross Total Resection of Malignant Glioma: Evaluation Using Mr Volumetric Study

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## Abstract

### Introduction

Malignant gliomas are highly infiltrative and aggressive primary brain tumors. Achieving gross total resection (GTR) using conventional white light microsurgical technique is a challenge. Five-aminolevulinic acid (5-ALA) can be used as an adjunct for the surgery of adult malignant glioma and improves the rate of gross total resection and patient survival. The use of this method in clinical practice is relatively new in Malaysia. We evaluate the extent of malignant glioma resection under fluorescence-guided resection (FGR) using volumetric MR neuroimaging.

### Methodology

A prospective pilot study was carried out in 5 newly diagnosed malignant glioma patients that underwent FGR using 5-ALA. All cases were subjected to both pre and postoperative MR that was performed 72 hours prior to and post surgery. The volumetric assessment was performed using special software program. The Extent of Resection (EOR) was then classified into three categories: Gross total resection (GTR, >90% tumor removal), Subtotal resection (STR, resection of 10-90% of tumor) and Partial resection, <10% tumor removal)

### Results

Five patients (mean age 54 years, range 45–60 years), 3 males and 2 females were recruited and analysed. These patients harbored Grade IV glioblastoma. The location of the tumor was predominantly in the frontal lobe (n =3, 60%). The median preoperative tumor volume was 35.67cm<sup>3</sup> (range 19.4-95.79) and the median postoperative tumor volume was 1.47cm<sup>3</sup> (range 0.12-2.37). GTR of >90% was achieved in all 5 patients.

### Conclusion

Our experience using Fluorescence-guided surgery enabled a GTR in 100% patients with glioma. We advocate increasing the sample size, which in turn will increase the power of the statistical analysis. The application of 5-ALA has a great potential as a novel standard in neurosurgery in Malaysia to maximize tumor resections for malignant gliomas.

**Keywords:** 5-Aminolevulinic Acid; Glioma; GBM; Fluorescence-Guided Surgery

### Introduction

Malignant gliomas and metastasis are the two most common intracranial lesions encountered in the neurosurgical routine<sup>1</sup>. High-grade malignant gliomas are the most common primary brain tumors in adults<sup>2</sup>. Gliomas are tumors, which arise from astrocytes

and are highly malignant as the cells reproduce quickly and are nourished by an ample network of blood vessels. As gliomas have finger-like tentacles, they are extremely difficult to remove completely. This becomes a problem especially when they are growing near eloquent areas of brain, which control important functions such as language and coordination. Based on WHO classification, malignant gliomas are comprised of anaplastic astrocytoma (WHO grade III) and glioblastoma (WHO grade IV)<sup>3</sup>.

Malignant gliomas may develop at all ages, the peak incidence being in the fifth and sixth decades<sup>4</sup>.

Although gliomas rarely metastasizes, they are notoriously invasive tumors and usually spread nearby along the axonal and basal membrane-like structures, where invasive tumor cells have often been identified few centimeters away from the enhancing tumor mass and even on the contralateral side of the brain. The characteristics of glioma cells, which include very high proliferation rate, genetic variability and discernible invasive tendency, leave very few options for therapy. Complete surgical removal of the tumor is key to Improved patient prognosis<sup>5</sup>.

Hence the only accepted strategy as far as surgery is concerned is achieving gross debulking of the tumour. The aim of surgery is to remove as much of the tumour as possible while preserving the neighbouring healthy brain tissue. Removal is often complicated by the nature of the tumor especially if the tumor is invasive and doing a complete removal can be difficult. One and two-year survival rates of high grade glioma patients are only 53.7% and 14.6% respectively<sup>6</sup>. A significant survival advantage was associated with resection of 98% or more of the tumor volume<sup>7</sup>.

Gross tumor resection (GTR) has been reported to be one of the most important factors affecting the prognosis and survival rate of glioma patients. Due to the infiltrating nature of glioma GTR remains a notorious challenge to neurosurgeons to distinguish between the tumor boundary and the surrounding edematous brain parenchyma. This can result in unintentional removal of healthy tissue or failure to remove malignant tissue<sup>8,9</sup>. In subtotal resection of glioma postoperative magnetic resonance (MR) images have revealed residual contrast enhancement at the resection margins, showing the difficulty of precisely identifying between the areas of infiltration and edematous brain intraoperatively.

In recent years one of the most groundbreaking methods that has come to the forefront in the advancement of local control of glioma surgery is the use of 5-aminolevulinic acid (5-ALA) induced fluorescence to guide surgery. After systemic or topical administration of 5-ALA neoplastic cells synthesize abundant intra-cellular protoporphyrin IX (PpIX). The role of 5-ALA is not only important in resection of gliomas but also for intraoperative visu-

alization of anaplastic regions<sup>5</sup>.

During intraoperative tumor resection, brain shift complexes the accuracy of the neuronavigation system up to several centimeters. 5-ALA fluorescence guided surgery (FgS) of malignant gliomas allows real-time intraoperative assistance for visualization of the tumor. PpIX fluorescence permits differentiating normal tissue from tumor that is independent of neuronavigation and brain shift<sup>10</sup>.

## Materials and Methods

The objective of this study was to evaluate the extent of malignant glioma resection under fluorescence guided surgery using 5-ALA and performing early pre and postoperative MR neuroimaging in defining the volumetric extent of resection.

In this prospective study, patient's aged above 18 years of age who were able to give consent, with newly diagnosed high-grade supratentorial malignant glioma, and without previous treatment, intended for surgery were considered. Patients with hypersensitivity to porphyrins, porphyria, photosensitivity, exfoliative dermatitis, renal or hepatic impairment or other malignancies were excluded. Patients who were pregnant and unable to undergo MRI due to presence of cochlear implants, surgical metallic clips, cardiac pacemaker or any metallic foreign body were also excluded.

5-ALA (Gliolan) for FgS in malignant glioma is approved for all patients older than 18 years of age. 5-ALA is a natural metabolite in the hemoglobin metabolic pathway found in the body. After oral ingestion it is taken up by glioma cells as it penetrates the blood-brain barrier<sup>11</sup>. It is then metabolized into its fluorescent metabolite, protoporphyrin IX (PpIX). When excited with 405-nm wavelength blue light PpIX emits violet-red fluorescence<sup>12</sup>.

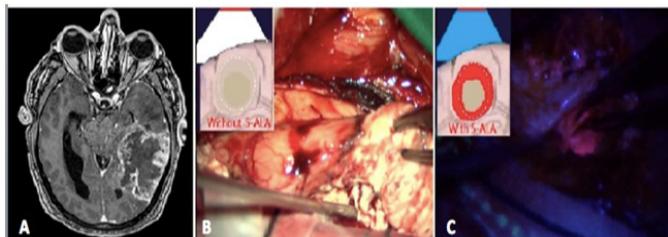
Excretion of PpIX is via a hepatic metabolism and normal serum PpIX levels are reached after 24 hours. Patients were protected against direct sun light the following day to prevent sun burns caused by the elevated PpIX in the patient's skin. Elevated liver enzymes can be found the following days.

The flow of surgery is barely disrupted as converting from standard white light to fluorescent mode on the microscope is achieved by the push of a button.

A prospective study was carried out in 5 newly diagnosed malignant glioma patients that underwent fluorescence guided surgery using 5-ALA. Oral administration of 5-ALA at 20 mg/kg body-weight, diluted in 50 mL of water 3h (range 2-4) before induction of anesthesia<sup>13</sup>.

Craniotomy was done following general anaesthesia. Surgery was then performed using a modified neurosurgical microscope (Leica), equipped with a fluorescence kit. Surgeons trained

in the use of 5-ALA carried out all operations. Each resection was initially performed using a conventional illumination. After the exeresis was judged as complete, the cavity was systematically inspected in the violet- pink light and with the neuronavigation system in order to identify any residual tumor.



**Fig.1** A. T1-weighted axial gadolinium-enhanced magnetic resonance image demonstrates an enhancing tumor (arrow) in the left temporal lobe. B. Intraoperatively using conventional white light illumination the infiltrative nature of the malignant glioma tumor (arrow) cells produces indistinct borders between normal and malignant tissues, and the lack of easily identifiable tumor margins confounds attempts at total resection C Under blue light illumination, using oral 5-ALA results in fluorescence of the malignant cells. The malignant cells appears pinkish (arrow) due to 5-ALA induced Protoporphyrin IX, thereby providing an opportunity for more complete tumor resection.

All cases were subjected to both pre and postoperative MR that was performed 72 hours prior to and post surgery. The tumor volume was defined as the volume of the enhancing regions including any rim enhancing necrotic or cystic components depicted on post contrast T1 MPRAGE sequence. Malignant gliomas on MR are depicted as well circumscribed tumors with regional necrosis surrounded by viable invading tissues and marginal contrast uptake<sup>14,15</sup>.

All patients were imaged using 1.5T Siemens AERA. Head coil was used in all patients. Prior to the scan patients were explained to about the procedure including possible risk of contrast material administration and written consent was taken in all cases.

The volumetric assessment was performed using OsiriX computed software program. After defining the border of the tumor as the region of interest on a slice-to-slice basis (axial plane) manually, this software program allowed for measurement of the total tumor volume. The slice thickness of the T1 MPRAGE images was 1.25mm.

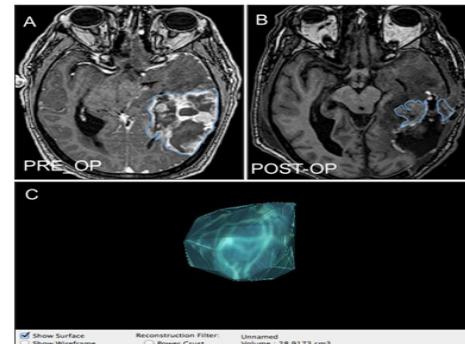
The Extent of Resection (EOR) was calculated using the following formula:

$$(\text{Preoperative total tumor volume} - \text{Postoperative total tumor volume})$$

Preoperative tumor volume x 100%

EOR was then classified into three categories: Gross total resection (GTR, >90% tumor removal), Subtotal resection (STR, resection of 10-90% of tumor) and Partial resection, <10% tumor removal). GTR is defined as absence of contrast uptake in the area of the GBM following resection, on post operative T1-weighted MRI obtained within 72 hours post surgery. If there was any doubt about the significance of a contrast-enhancing element, this was considered residual tumour.

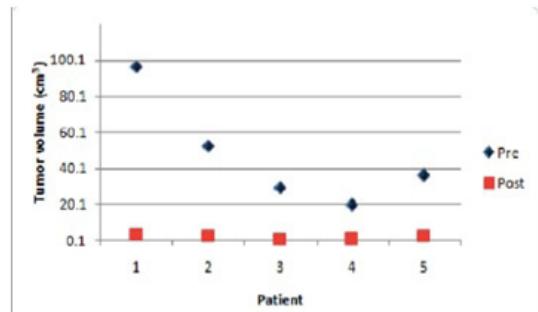
Two radiologists experienced in reporting MRI brain independently interpreted the images. In the event of a disagreement a third radiologist independently interpreted the images. Final report was then made by consensus. All radiologists were blinded from each other's report.



**Fig 2:** Selected axial T1-MPRAGE Post gadolinium MRI images of a glioblastoma multiforme pre-operatively (A) and post-operatively (B) together with (C) an example of volumetric reconstruction of selected section of a mass.

## Results

Five patients (mean age) of which 3 males and 2 females were recruited and analysed. The median age was 54 years (range 45–60 years). All the five patients were affected by newly diagnosed gliomas. Histopathological results revealed that all these patients harbored glioblastoma (WHO grade IV).



**Fig 3.** Preoperative and postoperative tumor volume.

The location of the tumor was predominantly in the frontal lobe (n =3, 60%). The median preoperative tumor volume was 35.67cm<sup>3</sup> (range 19.4-95.79) and the median postoperative tumor volume was 1.47cm<sup>3</sup> (range 0.12-2.37). The Gross total resection (GTR) of >90% was achieved in all 5 patients.

Patient No	1	2	3	4	5
Age	60	59	51	55	45
Sex	Male	Male	Female	Female	Male
Location	Temporo-Parietal	Temporal	Frontal	Frontal	Fronto-Parietal
Histo-Pa-thology	Glioblastoma	Glio-blastoma	Glio-blastoma	Glio-blastoma	Glioblastoma
Extent of Resection (%)	97.5	96.8	99.6	98.5	95.9

**Table 1:** Patient Demographic and Clinical characteristics.

## Discussion

Maximal possible cytoreduction without incurring neurological deficit in malignant glioma surgery is an independent prognostic factor. Aside from that GTR is an independent prognostic factor for survival in GBM and time to tumor progression (TTP). GTR of 98% and more is considered to have the better prognosis following GBM resection and is best assessed on pre and post surgery MRI.

Previous studies have shown that the rate of complete resection using conventional white light microsurgical technique varies between 23-36%. In our study, GTR of >90% was achieved in all 5 patients. Oral administration of 5-ALA increases the extent of resection, as switching to violet-blue light illumination intra-operatively allows the neurosurgeon to better distinguish the glioma margin from normal brain parenchyma. Complete resection results in improved patient survival and greater response to adjuvant therapies. For detection of residual tumour, early postoperative MR can avoid benign enhancement of surgical site caused by blood-brain barrier disruption, surgical manipulation, postoperative inflammation and luxury perfusion. Therefore, it is recommended that early postoperative MR be performed within the first 3 days following surgery, hence minimizing interpretation inaccuracies caused by surgical artifacts, as decision of further therapy is highly dependent on accurate post-operative assessment.

A limitation of FgS is that high-grade glioma is often a heterogeneous tumour consisting of areas of highly proliferative region, low-grade differentiation and necrosis. The areas of low-grade differentiation and necrosis will not show PpIX fluorescence hence failing to meet the target of gross total removal in a reasonable number of cases.

## Conclusion

The findings in this study demonstrates the enormous potential of 5-ALA for visualization of tumor tissue intraoperatively. Fluorescence-guided surgery enabled a GTR in 100% patients. Performing early postoperative MR imaging yielded reliable and accurate information in detecting residual tumor. However due to small sample, the study was underpowered, and thus, did not reach statistical significance. We advocate to increase the sample size, which in turn will increase the power of the statistical analysis. The application of 5-ALA has a great potential as a novel standard in neurosurgery in Malaysia to maximize tumor resections for malignant gliomas.

## Conflicts of Interest

The authors declare no conflict of interest.

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