Revolutionizing Treatment of High-Grade Gliomas Through the Use of 5-Aminolevulinic Acid Fluorescence Guided Surgery

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Introduction

Adult glioma is a tumour occurring in the brain or spinal cord and originating from glial cells. For over two decades, no changes have been made to methods used in the treatment of adult gliomas. The most common type of gliomas, grade IV glioblastomas, continues to have a dismal prognosis, with an average survival time of only 8-12 months. However, recent studies suggest that the novel treatment technique 5-Aminolevulinic Acid (5-ALA) Fluorescence Guided Surgery (FGS) may be able to prolong average patient survival. 5-ALA is an orally administered compound which is easily metabolized by healthy cells, yet cannot be processed by tumour cells. Thus, it accumulates in malignant tumour cells and causes them to fluoresce under a modified microscope during surgery. It eradicates many of the limitations faced by neurosurgeons today such as the inability to distinguish tumour margins and a lack of real-time neuronavigation. 5-ALA may be the next step in revolutionizing the standard of care for high-grade glioma patients.

The current standard of care for gliomas includes maximum surgical resection, followed by adjuvant chemotherapy and radiotherapy. However, surgical resection often fails to remove large numbers of cells on the outer surface of the tumour, in favour of leaving as much healthy tissue as possible [1]. Furthermore, chemotherapeutic drugs are widely ineffective at destroying remaining tumour cells as the blood-brain barrier restricts access to the tumour. Doses large enough to completely destroy remnant cells of the tumour would also risk patient mortality due to vital organ damage. Unfortunately, because of the ineffectiveness of chemotherapeutic drugs currently available, if larger than 2% of the tumour is left behind, it is almost inevitable that the tumour will reoccur [2]. This further reduces the patient's survival time due to the need for repeated surgeries and excessive drug infusions. Thus, a significant portion of the tumour must be removed during the initial surgical resection in order to minimize reliance on chemotherapeutic agents. In this context, 5-ALA FGS offers several benefits compared to the current standard of care, such as greater visualization of tumour margins, real-time guidance and access to immediate grading of the tumour. Therefore, 5-ALA should be integrated as part of the standard of care for high-grade gliomas.

Tumour Margin Visualization

In order to give patients the best chance of survival, neurosurgeons aim to remove >98% of the tumour. Unfortunately, this goal is only achieved in approximately 35% of cases [2]. One reason for this is the difficulty in distinguishing the viable tumour from adjacent healthy cells using a traditional white light microscope. Gliomas grow diffusely, infiltrating surrounding tissue in small clumps of cells, therefore creating ill-defined edges. This can be overcome by 5-ALA as it causes the tumour to fluoresce, allowing clear visualization of tumour margins [3]. Originally discovered as a natural metabolite involved in the heme producing pathway of the body, the compound is able to bypass the blood-brain barrier as its molecules are small enough [4]. Currently, all synthetically developed drugs used in FGS have molecules that are far too large and are unable to infiltrate the brain [4]. 5-ALA's ability to enter the brain alongside its specificity in targeting malignant cells allows for precise resection of the tumour. Clinically, 5-ALA has consistently shown to fluoresce in 90% of malignant cells, leading neurosurgeons closer to the goal of removing >98% of the tumour [1].

The current standard of high-grade glioma care also heavily relies on MRI scans taken prior to surgery; used in addition to white light microscopy as a guide to identify a tumour's location and margins

intraoperatively. While this imaging is routinely practiced, it poses several problems that prevent complete surgical resection. MRI scans often fail to detect the outer edges of the tumour as high-grade gliomas infiltrate the surrounding tissue with low cell density [5]. However, 5-ALA has been shown to fluoresce within infiltrating cells at the edges of the tumour. Roessler et al. compared the sensitivity of 5-ALA to that of contrast-enhanced, finding that 5-ALA was able to detect tumour margins two times more frequently than MRI [6].

Brain Shifts

Another limitation of the routine use of pre-operative MRI scans is the major brain shifts that can occur during surgery. Opening the skull contributes to significant shifts due to the rushing of air into the brain cavity, making MRI scans taken prior to surgery a much less accurate guide [7]. Nimsky et al. conducted a study where pre- and post-operative MRI scans of 64 patients were taken, and overlaid, to compare any shifts in midline structures and tumour margins. A large variability in structure location was found when comparing pre- and post-operative scans; in fact, the outer layer of the cerebrum was displaced up to 24mm due to neuroanatomical shifts that followed craniotomy [7]. Currently, no models exist that can predict when or how such brain shifts occur. Therefore, given this structural displacement of the brain during surgery and the current lack of compensatory solutions for such shifts, pre-operative MRI scans are largely inaccurate when faced with the microscopic tumour margins that must be identified. 5-ALA provides real-time navigation to neurosurgeons as brain shift is no longer a concern. Due to its high sensitivity in identifying tumour margins missed by MRI scans and real time guidance, 5-ALA has increased complete resection rates significantly, from 35% to approximately 65% of patients [3]. A randomized trial with 322 glioma patients confirmed higher resection rates and therefore, higher progression-free survival in patients administered 5-ALA [3].

Histopathological Analysis

Gliomas are composed of heterogeneous cell populations with intertwined clusters of cells, all having progressed at various rates. This often leads to histological undergrading and therefore, lack of proper and immediate treatment such as chemotherapy [8]. Therefore, it is important that areas of highest malignancy, called anaplastic foci, are identified intraoperatively in order to be used as a sample for histopathological analysis. This permits the most accurate diagnosis and subsequently, the most patient-specific course of treatment. Currently, there is no reliable way of detecting such anaplastic foci in samples of the tumour obtained during surgery as MRI scans do not provide enough contrast to identify areas of high malignancy [8]. Thus, tumour biopsies are excised less precisely and are prone to many sampling errors. On the other hand, 5-ALA is able to detect anaplastic foci intraoperatively as it has shown preferential fluorescence accumulation in malignant cells (exact reasons remain unclear). For example, Widhalm et al. identified 5-ALA as a promising marker for anaplastic foci as fluorescence was observed in 89% of patients with grade III gliomas [8]. Use of 5-ALA for identification of anaplastic foci would also mean the immediate grading of the tumour as a larger volume of fluorescence indicates more malignancy and therefore, marks a higher grade. Immediate grading allows treatment to be initiated more effectively and without delay, while waiting for results to be confirmed by subsequent histopathological analysis.

Intraoperative Magnetic Resonance Imaging

Despite the identified benefits of 5-ALA in eradicating limitations faced by surgeons today, many still argue that intraoperative Magnetic Resonance Imaging (iMRI) is a more effective solution to improve resection outcomes. The equipment and training to carry out iMRI is currently available at all facilities and requires no further funding to carry out [5]. By using iMRI, the issue of brain shift is mitigated as MRI scans are taken after the brain cavity has been opened and all structural changes have already occurred [5]. Yet, issues regarding margin visualization and inability to detect anaplastic foci resolved by 5-ALA still persist. Furthermore, 5-ALA only accounts for a fraction of the cost of carrying out an MRI scan during surgery [9]. iMRI also disrupts the flow of surgery, prolonging the procedure for up to one hour [10]. Importantly, the risk of complications arises as the time of surgery increases, especially considering the majority of glioma patients are elderly and thus more susceptible. More research needs to be done on the specific risks associated with using iMRI during glioma resections. Although iMRI poses a temporary solution, it still leaves many current issues unsolved such as the lack of real time intraoperative guidance and inability to identify areas of high malignancy. Proper training and implementation of 5-ALA, on the contrary, have far more potential than iMRI in improving surgical resection rates and overall patient survival [10].

Conclusion

Overall, 5-ALA provides a unique and cost-effective solution for many issues faced by neurosurgeons today, marking one of the most important advances in the treatment of adult gliomas in the past two decades. It allows for increased surgical resection rates and thus, improved patient outcomes. Proper training of neurosurgeons in facilities should be implemented as a long-term solution, rather than temporary changes being made using existing and routine technologies such as iMRI. Consequently, 5-ALA should be integrated as part of the standard of care for high-grade gliomas. While surgical resection currently aims to only improve a patient's symptoms, 5-ALA could be the next step in allowing surgery to be used as a cure.

Word count: [1492]

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