

Awake magic: glioblastoma resection under 5-aminolevulinic acid guidance during awake craniotomy. A case report with video demonstration

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Abstract

An awake craniotomy's primary goal is to remove the tumor or damaged cells as much as possible without affecting the patient's capacity for clear thought or other crucial functions. This surgical procedure offers a better prognosis by balancing the maximum removal of lesions with the preservation of working zones. For patients with malignant gliomas, the current neurosurgical objective is to resection the large part of a tumor using contrast and not causing neurological deficits. Neurooncological patients are required to have further chemotherapy and radiotherapy, with a control MRI of the brain in 3 and 6 months. Real multidisciplinary work should be provided to improve each patient's quality of life and overall survival. This paper aims to report a single case of successful awake craniotomy with fluorescence guidance and discuss the outcomes of the performed surgery.

Keywords: awake craniotomy, gliolan, 5-aminolevulinic acid

Introduction

An *awake craniotomy* is a surgical procedure in which a patient is deliberately kept awake during the surgical process or a portion of the surgery [1]. The main objective of an awake craniotomy is to remove the tumor and preserve the patient's executive functions to think clearly and perform other essential duties. This surgery provides a better prognosis by balancing the maximal removal of the damaged cell structures while conserving functioning zones [2]. Maximal, safe contrast-enhancing tumor removal is the current neurosurgical priority for patients with malignant gliomas. However, only a small percentage of surgeons manage to remove the contrast-enhancing tumor completely [3]. This restriction is due, in part, to the difficulty of separating a living tumor from the nearby normal brain during surgery at the tumor boundary using traditional white-light microscopy. To get over this drawback, malignant gliomas are now treated with fluorescence-guided surgery (FGS) that makes use of 5-aminolevulinic acid (5-ALA). The use of FGS enables the intraoperative viewing of

malignant glioma tissue and provides the neurosurgeon with independent neuronavigation and brain shift real-time guidance for separating the tumor from the normal brain [4]. Corns et al. [5] demonstrated the safety of glial tumor resection with awake craniotomy with 5-aminolevulinic acid guidance; our case report includes a video of the resection¹.

Case Presentation

A right-handed female patient, 55 years old, was admitted to our hospital with complaints of dizziness, lethargy, general weakness, distraction, disorientation in space and time, and memory distortion. According to the patient, she has been ill since June 1, 2022, when the complaints mentioned above abruptly began. On June 6, 2022, she was rushed to a nearby hospital, where doctors decided to perform MRI scans of her brain. An MRI revealed the tumor in the left frontotemporal region. The patient was admitted to our hospital, where a detailed neurological examination was provided. On admission, the consciousness was clear, and the Glasgow Coma Score of 15

¹ The process of awake neurosurgery in our hospital is demonstrated here: <https://vimeo.com/896060075>.

points. She answered questions with slowness but answered some questions out of hand, sometimes corrected herself, and executed instructions. Although she was self-oriented, there was disorientation in space and time. Executive functions, criticism, and the adequacy of her condition were reduced. The Karnofsky Performance Score was 70%. A neurological examination of cranial nerves revealed central paresis of the right facial nerve (House-Brackmann score 3). Pharyngeal and palatine reflexes were reduced, with the soft palate and the tongue deviation to the right. Also, there were fibrillar twitches on the right half of the tongue. The speech therapist revealed dynamic aphasia of mild to moderate severity. Since our hospital started the project on glial tumors, we have provided 3T MRI examinations (Figure 1) for all patients with glial tumors; moreover, if we see that there is contrast enhancement, we do an operation with 5-aminolevulinic acid hydrochloride (GliolanR). Due to Broca area's involvement and risk of further deterioration of hemiparesis, the decision was made to perform an awake tumor removal. Specimens from the tumors are analyzed separately and are kept in our Biobank [6].

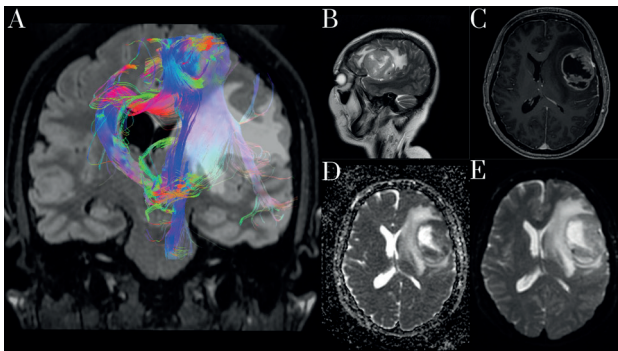


Figure 1 - A: DTI- MRI was performed and revealed displacement of corticospinal tracts on the left with the total destruction of associative and commissural pathways. B: T2WI that demonstrates the tumor in the left frontotemporal region, involving the speech center. C: Post-contrast images demonstrate enhancement, notice there was also a 13 mm dislocation of central structures. D and E: ADC (D) and DWI (E) images demonstrate the presence of areas of pronounced restriction of the diffusion coefficient in the tumor stroma. It presumes necrotic tissue in the tumor, which indicates a high-grade tumor.

Pre-operative preparation and surgery

The decision was made to use a neuronavigation system and mark the operation field on the projected image of the tumor (seen on video). The scalp block technique with 0.5% bupivacaine 40 ml was performed before Mayfield skull clamp placement. Sedation was achieved with 200 mg of dexmedetomidine and 0.2 mg of fentanyl, and we used the "asleep-awake-asleep" approach. Additionally, we used the local anesthetic during durotomy. To measure and view fluorescence working, a microscope called the Pentero 900 (Carl Zeiss Meditec AG, Obrekochen, Germany) with a fluorescent BLUE400 light module was employed. The surgery was performed with 5-ALA fluorescence and the speech and language therapist's control of the Broca center. Additionally, the patient was required to perform movements with the right hand and the right leg.

The tumor was meticulously removed using fluorescence, and all pathologic vessels were coagulated; however, there was a possibility to preserve functionally important vessels, as seen in the video. Because of the close relationship with Broca's area, when, during the operation, there were speech problems, the decision was made to stop the resection. Despite an intense residual fluorescence in Broca's region, resection was stopped because the patient experienced speech arrest during bipolar stimulation at a depth of the resection cavity.

Maximal resection and hemostasis were achieved, and the post-operative field was filled with hemostatic pads (Surgicel). The dura mater was tightly closed, and duraplasty was made. Muscles and skin were tightly sutured. The patient stayed in the intensive care unit for 1 day, and then, after a control post-operative CT, which showed a lesser deviation of the midline structures (Figure 2), the patient was transferred to the pathology department. The patient's speech and calculations improved, and she became more time-conscious.

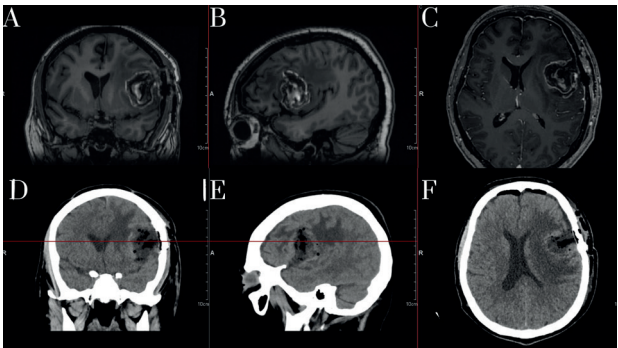


Figure 2 - A, B, C: Postoperative MRI demonstrates the contents of the signal intensity corresponding to the cerebrospinal fluid, with foci of high density on T1WI along the periphery of the bed and along the course of operative access, due to hemorrhagic and hemostatic components. D, E, and F postoperative CT scan demonstrates no apparent complication.

Histological findings

The glial fibrillary acidic protein (GFAP), a Ki-67 proliferation antigen, was detected using immunohistochemistry. IDH1 gene mutation, 1p-19q co-deletion status, ATRX gene mutation, and CDKN2A/2B gene mutation were all negative based on molecular genetic analysis. The presence of necrosis (Figure 3) and the morphological characteristics helped to confirm the diagnosis of glioblastoma, IDH-wildtype, WHO grade 4, and ICD-O code 9440/3.

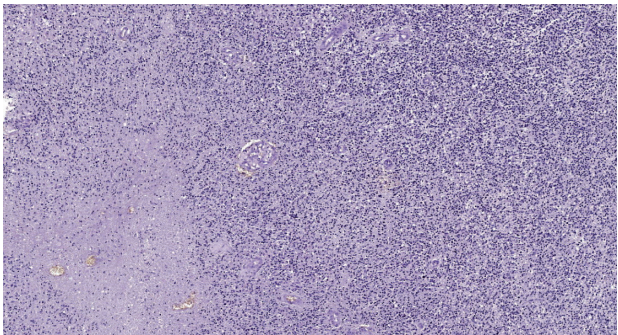


Figure 3 - Glioblastoma multiforme x 100. Stained with hematoxylin and eosin.

Three weeks after the operation, the patient was headed to the oncological treatment. Pre-treatment dosimetry planning was carried out on the TomoPlannig apparatus; the total radiotherapy dosage was counted as 60 Gy 5 times a week with a daily visual inspection. The patient also got the chemotherapy course, which consisted of a Temozolomide 140 mg per os daily. Three months later, after completion of radio and chemotherapy, the patient underwent a control MRI investigation with contrast (Figure 4).

The postoperative patient's Karnofsky Performance Score was 80%, and she started to work again as no neurological deficits were observed. Six months later, after another course of chemotherapy, there was thrombocytopenia; due to this diagnosis, the patient was temporarily withdrawn from the

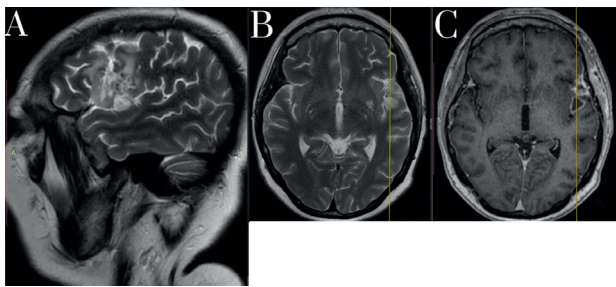


Figure 4 - 3 months follow-up MRI examination with contrast. A: Sagittal T2 Propeller view with an apparent decrease of enhancement. B: Axial T2 Propeller. C: Axial T1 fat-suppressed fast spoiled gradient echo with contrast enhancement on the periphery demonstrates slight residual tissue, not expanded over time.

treatment. After the course of virus-inactivated thrombocyte transfusion, her thrombocyte level eventually increased. The patient developed continued growth of glioblastoma at nine months, muscle strength of right limbs reduced to 3 points, and criticism reduced as well. She underwent one more resection surgery of the tumor of the left frontotemporal region using fluorescence. After her last operation, she has undergone one more chemotherapy cycle. The patient is alive at 1-year follow-up.

Discussion

Currently, the "gold standard" for the excision of tumors or lesions in or close to eloquent brain areas is awake craniotomy with brain imaging [7]. Excision of or damage to regions necessary for speech and motor control skills may result in severe neurological impairments. In 278 patients, Zhang et al. discovered a link between an awake craniotomy and a low rate of postoperative neurological deficits and gross total resection of tumors [2]. In Della Puppa et al.'s study, 31 patients underwent 5-ALA fluoresce surgery; after a 90-day assessment, there was a 3% rate of significant morbidity, and it is crucial to remember that 0% of patients who underwent surgery while awake presented with permanent morbidity [8]. Fluorescence guidance allows for visualization of the tumor extent and can provide information about vascular structures [9]. The unprecedentedly high sensitivity, specificity, and positive predictive value of tissue fluorescence following an oral dose of 5-ALA can provide information about tumor grade even during surgery [1, 10]. Postoperative MRI showed gross total resection was completed in 86% of surgeries operated with 5 ALA [11]. Neurocognitive functions should be evaluated before, during, and after surgery to predict the results and the outlook [12]. Due to preserved neurocognitive functions, 97% of patients who underwent awake surgery for an accidental low-grade glioma returned to work, highlighting the need for comprehensive intraoperative mapping to maintain a better quality of life [13]. Since the first description in the 19th century, different anesthesia methods have been suggested. Dr. Picconi, in his work [14], describes the method of asleep-awake-asleep as the safest one for brain mapping but mentions it requires excellent anesthesiology techniques to perform. According to Goettel et al., dexmedetomidine was as effective as propofol-remifentanyl in sedating patients during awake craniotomy for supratentorial tumor removal. Dexmedetomidine was linked to fewer adverse respiratory events as well [15]. 93% of the patients underwent a gross full resection or a near-gross total resection, which is an optimal amount of resection [15].

The challenges of awake surgery with 5-ALA guidance could arise in the absence of fluorescence. In patients with

cortical mapping and 5-ALA guidance, fluorescence was present in 50% of cases [11]. Only 12% of awake craniotomy patients demonstrated neurological complications that were either new or deteriorated from their previous deficiencies; however, 8% recovered within two months after the operation [15]. Transient aphasia developed in 14 patients, and permanent aphasia developed in 4 patients [11].

The right patient selection and patient counseling are crucial. Brain mapping requires a cooperative patient who can follow instructions during surgery; as a result, choosing the wrong patient might lead to an unsuccessful awake craniotomy [12]. Different authors proposed different approaches for awake neurosurgery [3]. However, our hospital prefers a combination of 5-aminolevulinic acid with awake neurosurgery. In the recent research of Gandhi et al., a comparative subgroup analysis of 5-ALA-guided versus traditional surgery revealed a 26% higher gross total resection rate in the 5-ALA subgroup [16]. A specialized biobank is essential in prospective oncological analysis. Our country's biobank [6] has been functional since 2018, and nowadays, we have more than 269 patients. Future research will be published in the future with details.

It will be possible to conduct a more in-depth study into the risk factors for various cancer subtypes, as well as provide appropriate prognostic indicators for survival and pharmacogenomics research with the use of biobank databases [17]. The research using data from the UK Biobank has discovered new susceptibility loci for certain malignancies, such as endometrial cancer, colon cancer, and cervical cancer - these studies are found to help comprehend the biochemical processes that underlie the growth of cancer [17].

Biobanks have been widely used for cancer prevention, diagnosis, and treatment and have been integrated into personalized medicine. Biobanks will unquestionably revolutionize research, enhance genetic research, and lead to the identification of new therapeutic targets [18]. IDH1 gene mutation, 1p-19q co-deletion status, ATRX gene mutation, and CDKN2A/2B gene mutation can be aimed in the future interdisciplinary oncology treatment of glioblastoma patients, which hopefully will increase their median survival.

It is currently proven that glioblastoma patients, in comparison to chemotherapy, surgical resection, or radiation alone, benefit from combination therapy, such as surgery or radiotherapy with chemotherapy, which may increase the likelihood of survival [19].

The paper reports on the excision of tumors by successful awake craniotomy with 5-ALA guidance and discusses the advantages and main challenges of this method. The paper considers only one case and builds assumptions around it. The awake craniotomy surgery is not performed frequently in our center; therefore, other literature reviews and case reports should be carefully considered.

Conclusion

Awake craniotomy with 5-ALA staining guidance maximizes the chances of gross total resection of infiltrative gliomas with visible fluorescence, allowing excision that would otherwise be missed without contrast, and aids in preserving executive and motor functions of the patients. Due to its high sensitivity and specificity, awake neurosurgery is considered potentially safe when combined with 5-aminolevulinic acid, and it provides maximal resection with vascular preservation. A multidisciplinary approach is essential in high-grade glial tumors. Specialized Biobank of CNS tumors will improve the quality of life and extend the life of neurosurgical patients.

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