

FIRST EXPERIENCE USING 5-ALA FOR HIGH GRADE GLIOMAS IN THE ALMENARA HOSPITAL

Primera experiencia del uso del 5-ALA en gliomas cerebrales de alto grado en el Hospital Almenara

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ABSTRACT

Introduction: The most frequent brain tumors in adults are high-grade gliomas and meningiomas. Having a discouraging prognosis of high-grade gliomas and knowing that the prognosis improves depending on the degree of tumor resection, is that new therapeutic strategies are sought, one of them is the use of 5-aminolevulinic acid (5-ALA) thanks to the fluorescence it produce in the tumor it allows to improve the rate of tumor resection, finally improving the prognosis of the patients. We presented the first experience in Almenara Hospital of the use of 5-ALA in a patient with a diagnosis of high-grade glioma.

Clinical Case: Presents itself the case of a 48-year-old male patient with clinical evidence of motor and sensory deficit contralateral to the lesion, without alteration of the state of consciousness. The magnetic resonance of the encephalon with contrast, a right frontal lesion is evidenced compatible with high-grade glioma. Therefore, it is programmed for guided surgery with fluorescence, where 5-ALA is used, and a total resection of the tumor is performed, obtaining an anaplastic ependymoma as pathological anatomy. The patient presented an increase in the motor deficit, which he later recovered. In the tomographic control with contrast at 4 months, complete tumor resection is evident.

Conclusion: 5-aminolevulinic acid is a drug that helps to properly delimit the edges of a high-grade glioma, by using a modified microscope, and thus increases the degree of tumor resection, ultimately improving the prognosis of the disease.

Keywords: Glioma, Aminolevulinic acid, Ependymoma, Fluorescence, Prognosis. (Source: MeSH NLM)

RESUMEN

Introducción: Los tumores cerebrales más frecuentes en el adulto son los gliomas de alto grado y meningiomas. Teniendo un pronóstico desalentador los gliomas de alto grado, y sabiendo que el pronóstico mejora dependiendo del grado de resección tumoral, es que se buscan nuevas estrategias terapéuticas, una de ellas es el uso del ácido 5-aminolevulinico (5-ALA) que gracias a la fluorescencia que produce en el tumor permite mejorar el grado de resección tumoral, mejorando finalmente el pronóstico de los pacientes. Se presenta la primera experiencia en el Hospital Almenara, del uso del 5-ALA en un paciente con diagnóstico de glioma de alto grado.

Caso Clínico: Se presenta el caso de un paciente varón de 48 años, con clínica de déficit motor y sensitivo contralateral a la lesión, sin alteración del estado de conciencia, con resonancia magnética de encéfalo con contraste se evidencia una lesión frontal derecha compatible con glioma de alto grado. Por ello se programa para cirugía guiada con fluorescencia, donde se usa 5-ALA, y se realiza resección total del tumor, obteniendo como diagnóstico anatomo patológico un ependimoma anaplásico. El paciente presentó aumento del déficit motor, que luego recuperó. En el control tomográfico con contraste a los 4 meses se evidencia resección tumoral completa.

Conclusión: El ácido 5-aminolevulinico, es un fármaco que ayuda a delimitar de manera adecuada los bordes de un glioma de alto grado, al usar un microscopio modificado, y así aumenta el grado de resección tumoral, mejorando finalmente el pronóstico de la enfermedad.

Palabras Clave: Glioma, Ácido Aminolevulinico, Ependimoma, Fluorescencia, Pronóstico. (Fuente: DeCS Bireme)

<https://doi.org/10.53668/2019.PJNS11057>

Peru J Neurosurg 2019, 1 (1): 21-26

High grade gliomas are one of the most frequent brain tumors, Ependymoma being one of them. In general, the life

prognosis of patients who present it is not good and this depends to a large extent on the degree of tumor resection. However, the infiltrative nature of the malignant gliomas makes the complete resection a challenge for the neurosurgeon because the boundaries between tumor tissue and normal tissue are not easy to identify by the human eye.

Submitted : October 26, 2018

Accepted : December 12, 2018

HOW TO CITE THIS ARTICLE: Vargas J, Palacios F, Romero E. First experience using 5-ALA for high grade Gliomas in the Almenara Hospital. *Peru J Neurosurg* 2019; 1(1): 21-26. doi:10.53668/2019.PJNS11057

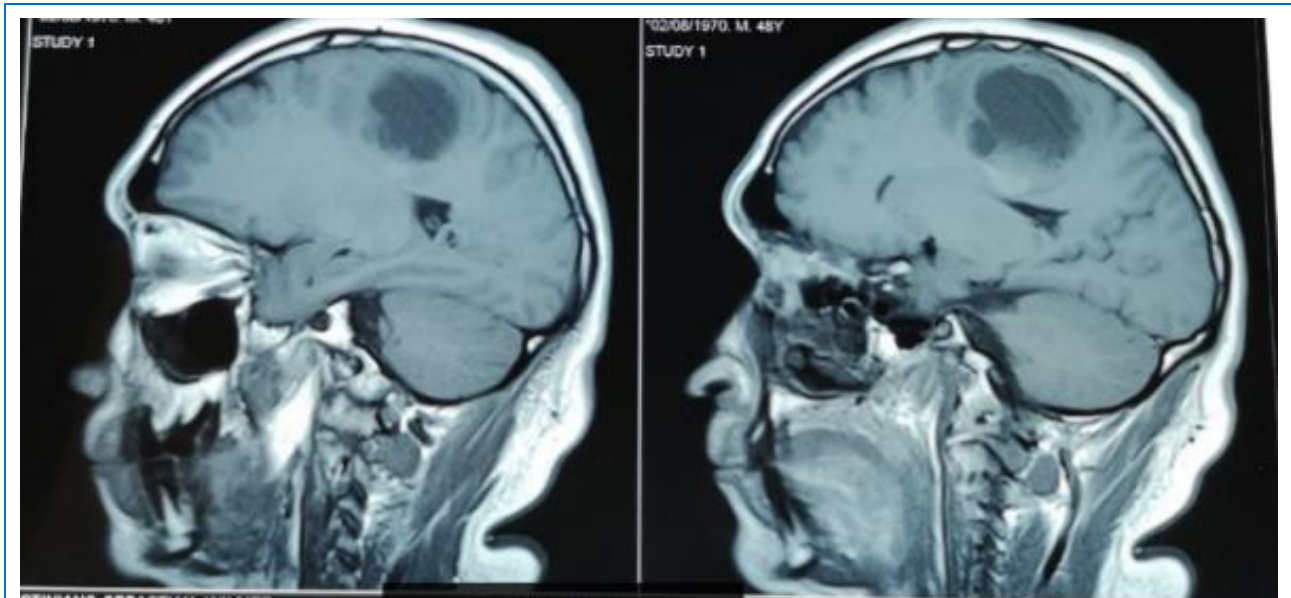


Fig 1. MRI of the brain without contrast in sequence T1 (sagittal view), showing evidence of an expansive hypodense process at the level of right precentral Gyrus, with an apparent nodule closely to the roof of the right lateral ventricle.

Recently, a novel technique of tumor identification during surgery is being used, this is based on the use of 5-ALA, a metabolite of hemoglobin, which generates more fluorescence in the tumor allowing a better visualization of this and therefore improving the degree of resection.

We present the case of a fluorescence-guided surgery with a modified microscope using 5-ALA in the resection of an anaplastic Ependymoma for the first time in our Hospital.

CLINICAL CASE

History and examination: 48-year-old male patient, native of Lima and from Cerro de Pasco, with no medical or surgical history of importance, with a 4-month history of disease characterized by oppressive sporadic pain in the lower left limb (MII) of intensity 2/10, which gave way spontaneously. At 3 months, a decrease in muscle strength is added in MII with difficulty in walking, so a request is made for a magnetic resonance imagen of the brain with

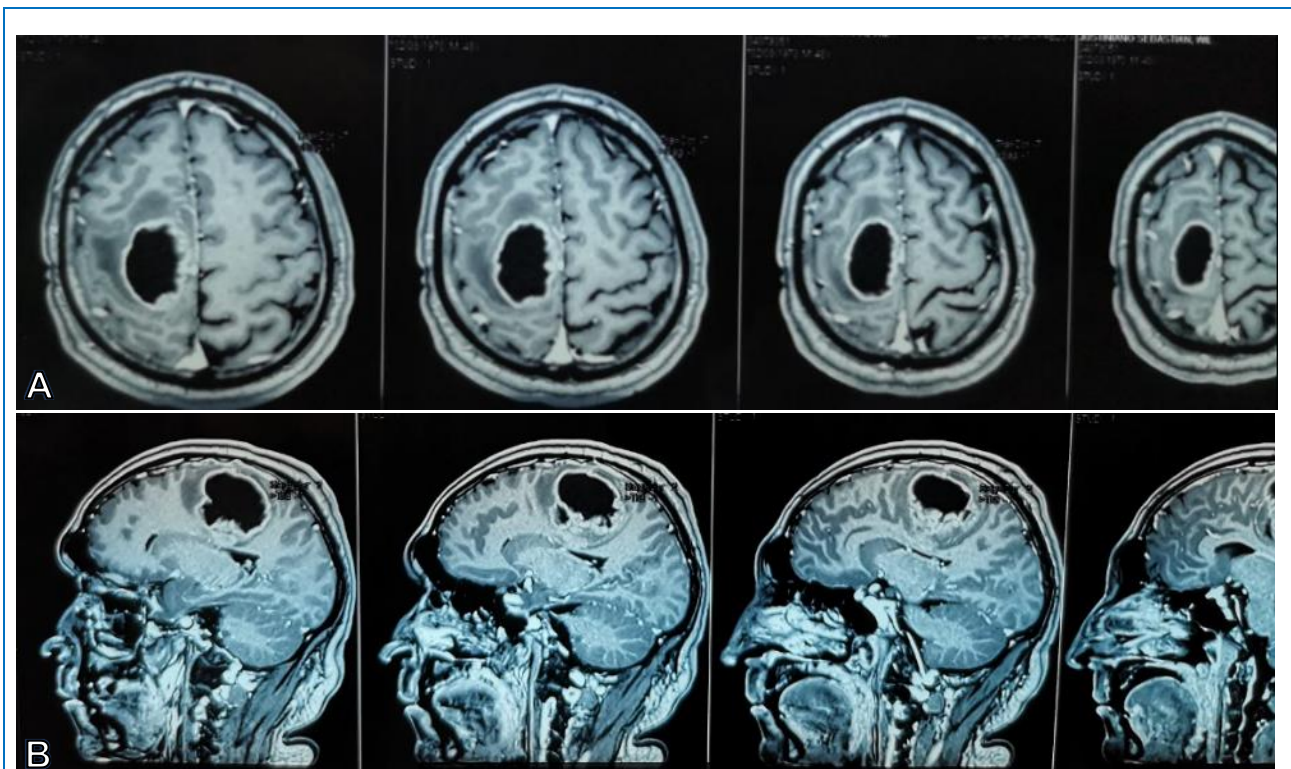


Fig 2. MRI of the brain with contrast in T1 sequence. **(A)** Axial section, showing an expansive process at the level of the right precentral gyrus with central necrosis and contrast ring uptake. **(B)** Sagittal section, showing an expansive process in the right precentral gyrus, with a contrast hypercaptating nodule close to the roof of the right lateral ventricle.

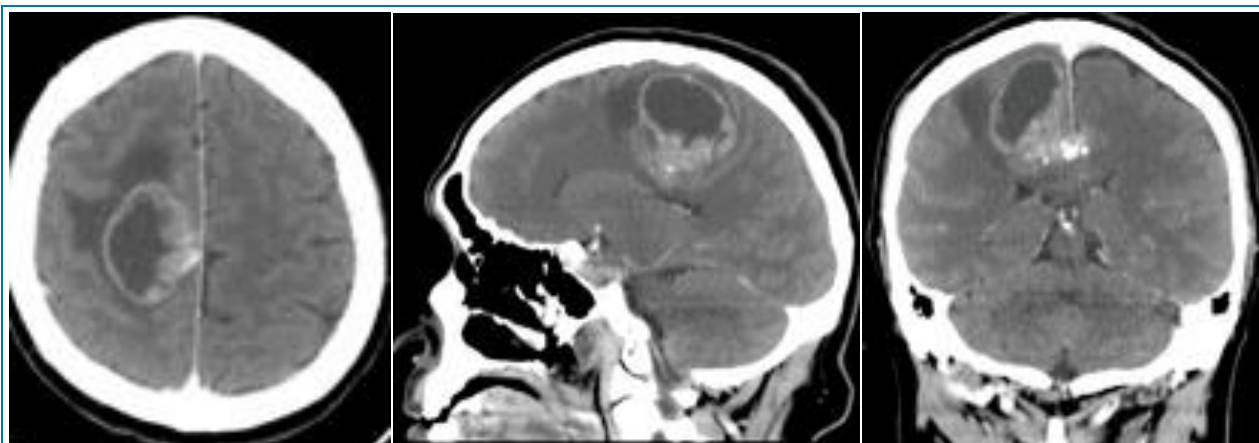


Fig 3. Brain CT with contrast, the left image in axial section, the middle in sagittal section and the right in coronal section, where the right frontal expansive process is evidenced with uptaking ring and a hypercaptating nodule with intralesional calcifications, in close relation with the roof of the right lateral ventricle.

contrast showing a right frontal expansive process (4.2x3.32cm PAXT) at the level of the pre-central, subcortical, hypodense in T1 that captures ring contrast, with central necrosis and a nodular component in the medial region (1.95x1.52cm PAXT) at the level of the roof of the right lateral ventricle, 0.5cm from the midline, without generating deviation from it, with moderate perilesional edema and with basal cisterns present (**Fig. 1 and 2**). A computerized axial tomography (CT) with contrast is performed, where findings like those of MRI are found in addition to calcifications in the tumor nodule (**Fig. 3**). Studies are also carried out to rule out metastases such as a thoraco-abdomino-pelvic CT with contrast and serum tumor markers, which were negative for neoplasms.

On physical examination, the patient was on the Glasgow scale of 15 points, without meningeal signs, with left hemiparesis to crural predominance (Brachial Daniels 3/5, crural Daniels 2/5), left hem-ihipoesthesia, central pupils, isochoric and photoreactive, with preserved osteotendinous reflexes, preserved cranial nerves.

Treatment: The diagnosis of right frontal expansive process was posed, probable high-grade glioma and was scheduled for surgery with a right frontal craniotomy, resecting the tumor under microscopic vision using 5-

amino-levulinic acid (5-ALA) as a visual aid; a dose of 20mg /kg of the drug was administered 4 hours before starting the brain dissection to show the neoplastic lesion. During the intraoperative period, a guided ultraviolet light dissection was carried out until the lesion was reached, with the reddish neoplastic tissue being appreciated (**Fig. 4 and 5**).

Evolution: Patient left the operating room extubated and went to the Neurosurgical Intensive Care Unit, with Glasgow scale at 15 points, without meningeal signs, with left hemiparesis that had increased to 1/5 in both superior limbs and inferior limbs. A cerebral TAC without contrast was performed in the immediate postoperative period, which showed total excision of the expansive process with little bleeding from the operative bed (**Fig. 6A**). On the 2nd postoperative day, intensive physical therapy was initiated, achieving a significant improvement in the motor deficit on the 7th postoperative day, leaving high with left hemiparesis 3/5.

The anatomo-pathological study reported an anaplastic ependymoma with clear cell pattern as definitive diagnosis, for which radiotherapy and adjuvant chemotherapy were initiated.

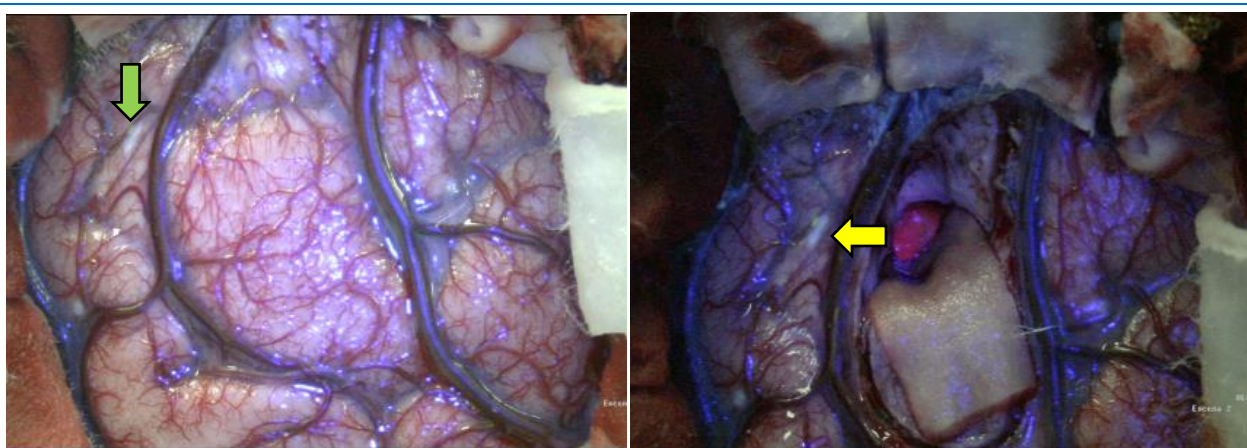


Fig 4. The left image shows the precentral gyrus (green arrow) where the lesion would be found according to the previous images, however, under ultraviolet light it is not possible to evidence red tissue suggestive of neoplastic tissue. In the right image, a reddish tissue suggestive of neoplasia is evidenced in the fundus (yellow arrow) under ultraviolet light, after dissecting to reach the lesion.

A control was performed 6 months after surgery, where a brain CT scan was performed with contrast, where no residual tumor was seen (**Fig. 6B**). Clinically, the patient was on a Glasgow 15 scale, without meningeal signs, with left hemiparesis 4/5, mild left hemi-hipoesthesia, isochoric and photoreactive pupils, wandering without support, preserved cranial nerves.

DISCUSSION

The incidence of primary malignant brain tumors is 3.7 / 100,000 in men and 2.6 / 100,000 for women, and in adults the most frequent brain tumors are high grade glioma (30.5%) and meningiomas (29.4%). High-grade astrocytomas, high-grade oligodendrogliomas, high-grade

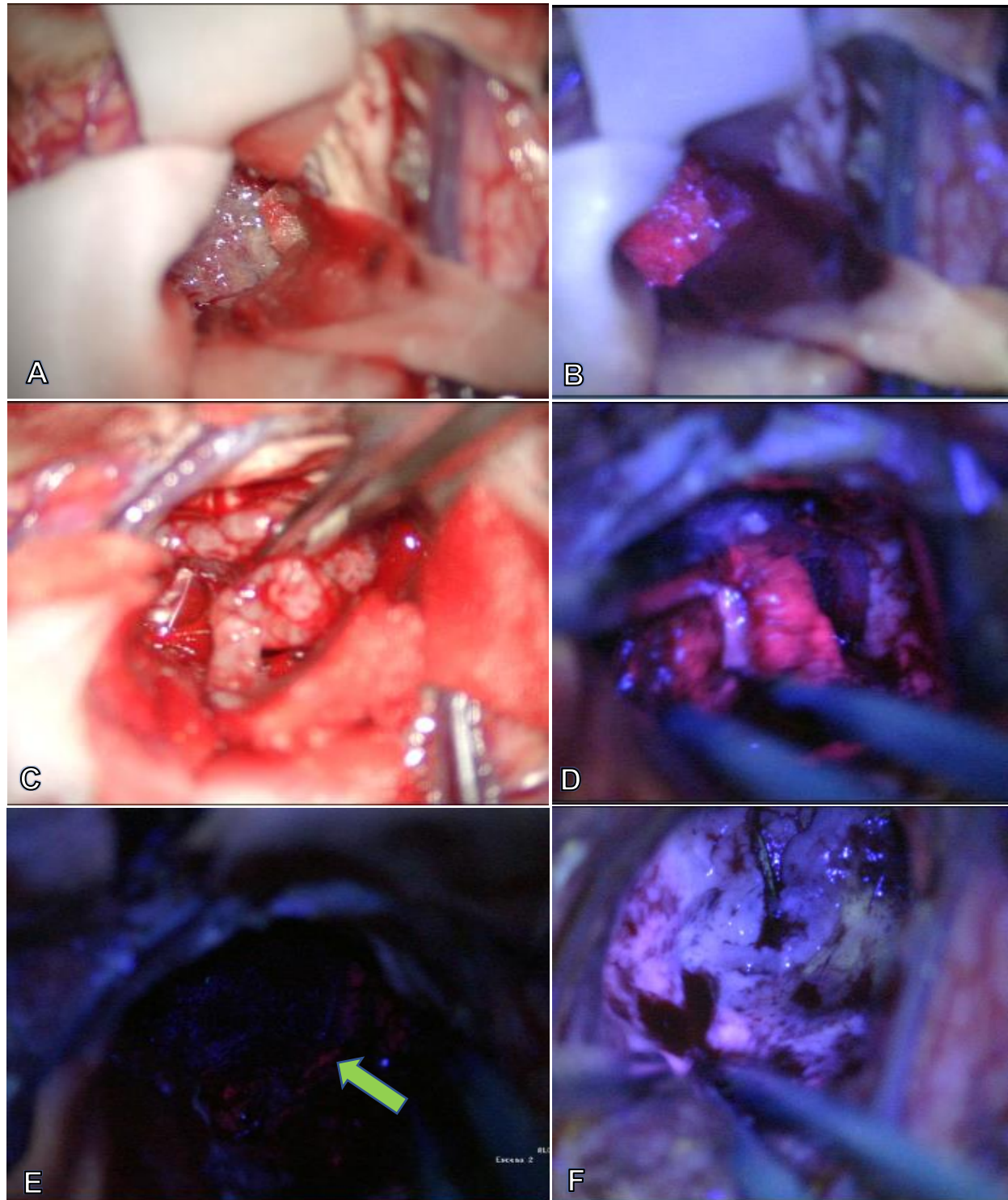


Fig 5. Intraoperative images. (**A and B**) correspond to the same operative moment, in **A** with normal light and in **B** with ultraviolet light, both show neoplastic tissue corresponding to the inferior wall of the lesion. (**C and D**) correspond to the same operative moment, in **C** with normal light and in **D** with ultraviolet light, both show neoplastic tissue in the medial wall of the lesion. (**E and F**) Intraoperative images of the end of the surgery, in **E** there are few remaining fragments of reddish neoplastic tissue (arrow) that were extracted, in **F** final operative bed where no red tissue suggestive of neoplasia is evidenced.

ependymomas, and mixed tumors are among high-grade gliomas ¹. In general, the prognosis is not good despite treatments, and it is diagnosed in the sixth and seventh decade of life, and complete resection increases efficacy of adjuvant treatments, such as chemotherapy and radiotherapy ².

Unfortunately, the fact that malignant gliomas have an infiltrating nature, makes it a challenge for the neurosurgeon, due to the difficulty of complete cytoreduction, because tumor margins are confused with normal brain tumors. That is why new techniques are created to improve the degree of tumor resection, and one of these techniques is the use of 5-aminolevulinic acid (5-ALA) and fluorescence-guided surgery with a modified microscope ².

5-ALA is a natural metabolite that occurs in the metabolic pathway of hemoglobin. Exogenous 5-ALA administered orally penetrates the blood-brain barrier and accumulates in the cells of the malignant tumor of the brain, since this drug is metabolized to protoporphyrin IX, which is fluorescent and violet red is visualized under ultraviolet light. 5-ALA preferentially accumulates in malignant glioma cells, and this depends on cell density, proliferative activity, neovascularization and permeability of the blood-brain barrier. To this end, 5-ALA is given 4 hours before cerebral dissection, orally, at a dose of 20 mg / kg, taking all precautions of photosensitivity, because at that time adequate serum values are reached.

In 2006, Stummer and colleagues, in the first phase 3 study on resection and prognosis in patients with high-grade glioma surgery assisted with 5-ALA, found that total tumor resection was achieved up to 65% patients in whom 5-ALA was used, versus 36% in patients who went to conventional surgery. For this reason, it is currently proposed, with a level of evidence 2b, that assisted surgery with 5-ALA is more effective than conventional surgery for the extension of tumor resection and increases the patient's survival time ⁴.

In our case, the patient had an anaplastic ependymoma which is a high-grade tumor, according to the WHO classification. Burford et al, found in their study that Anaplastic Ependymoma (WHO grade III) had a high affinity for the drug, in such a way that it showed great fluorescence ¹⁶.

Chohan et al, in their study found that, during the intraoperative, a high fluorescence signal has a high correlation with the presence of tumor cells in recurrent high-grade gliomas, which gives the use of 5-ALA a high value positive predictive ¹⁷.

On the other hand, Teixidor et al, achieved a complete resection in 54% of patients, without the presence of adverse effects, and neurosurgeons considered that the use of ALA was optimal in 60% of patients ².

It is clear that there is statistically significant evidence to use 5-ALA in high-grade gliomas, and thus achieve a better degree of tumor resection; This indirectly implies an increase in the efficacy of adjuvant therapies (chemotherapy

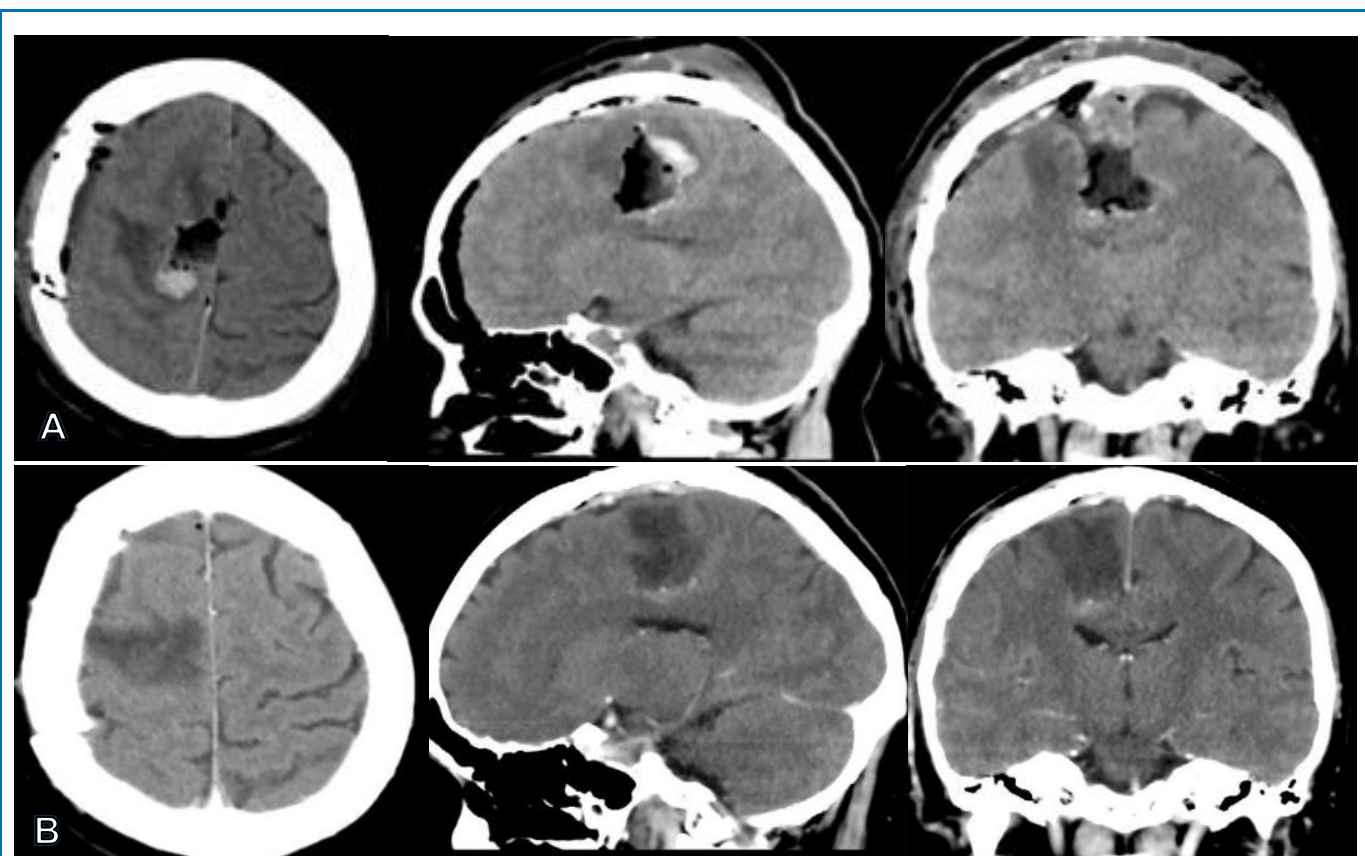


Fig 6. (A) Cerebral CT without contrast, in the immediate postoperative period (axial, sagittal and coronal section), where complete exeresis of the expansive process is evidenced, with little bleeding in the operative bed. **(B)** Cerebral CT with contrast, AT 6th postoperative month (axial, sagittal and coronal section) where total excision of the expansive process is demonstrated with right frontal malacia.

and radiotherapy), and subsequently an improvement in the survival of patients with high-grade gliomas.

In Peru's social insurance, surgery has not yet been performed with the help of this drug, this being the first report of the use of 5-ALA in tumor surgery at Almenara Hospital. The introduction of this drug in the national request is expected soon in order to be used in daily surgical practice and thus be able to perform a prospective study and determine the effectiveness rates of 5-ALA in the resection of high-grade gliomas in our medium.

CONCLUSION

It is concluded that 5-aminolevulinic acid is a drug that helps to adequately delimit the edges of a high-grade glioma when using a modified microscope, thus increasing the degree of tumor resection and finally improving the prognosis of the disease by improving indirectly the efficacy of adjuvant therapies. Therefore, the 5-ALA should be included in the national social insurance request, to be used in patients who meet criteria, and thus improve the care of this type of patients.

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Disclosures

The authors report that 5-ALA material was donated for the study by the supplier company of the microscope, but that it did not participate in the study or in the specific findings of the same.

Authors Contributions

Conception and design: Vargas J, Palacios F, Romero E. *Drafting the article:* Vargas J. *Critically revising the article:* Vargas J, Palacios F. *Reviewed submitted version of manuscript:* Vargas J. *Approved the final version of the manuscript on behalf of all authors:* Vargas J.

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