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Chapter

Neurosurgical Tools to Improve Safety and Survival in Patients with Intracranial Tumors: Neuronavigation, MRI, and 5-ALA

Luis Fernando Moura da Silva,
Guilherme Augusto de Souza Machado and Ricardo Ramina

Abstract

This chapter describes the usefulness of surgical technologies such as intraoperative MRI, 5-ALA fluorescence-guided surgery, and neuronavigation as tools to make brain tumor resections safer and more effective. The focuses are practical aspects and the relevant literature regarding the impact of their use in avoidance of complications, improvement in survival rates, and some tips and tricks acquired in the experience of our department. All three strategies have an important role in neuro-oncological surgery. The future probably will prove that the combination of these tools, selected case by case, is the best way to achieve the best results regarding safety and effectiveness.

Keywords: neurosurgical procedures, brain neoplasms, neuronavigation, fluorescence-guided surgery, magnetic resonance imaging

1. Introduction

In all areas of science and knowledge, technology development is thought to bring solutions that optimize process, reduce costs, and make things safer. Brain tumor resection is a routine procedure in neurosurgical practice. In most of the cases, complete surgical resection remains as the gold standard of treatment. But some cases are real challenges to the neurosurgical team. Deep-seated tumors demand planned pathways to achieve it considering functions of each area of the brain, including white fiber tracts to avoid injury related to the approach. Besides eloquent area involvement, in some cases, despite simple or complex approaches, some aspects of the lesion turns them more difficult to resect such as its consistency, adherence to neighboring structures, and the presence of a well-defined cleavage plan. Neurosurgery has this cardinal aspect that every structure matters and injuries can bring catastrophic consequences.

Depending on the aggressiveness of the tumor, the tolerance to incomplete resection changes. But, for example, in benign tumors with incomplete resection, remnants can be followed by the "watch-and-wait" policy. Only in case of progression, a new decision should be done: reoperation, complementary treatment such

as radiosurgery, radiotherapy, chemotherapy, or immunotherapy (depending on its characteristics). In cases of malignant tumors such as gliomas and metastasis, the extent of resection (EOR) is directly related to recurrence and survival. Incomplete resection for these patients should be only discussed if the risk of neurological injury is high. Obviously, *not to harm* is always the most important principle. Increase in survival only makes sense if accompanied by quality.

Even with intense microsurgical training, the multidisciplinary treatment challenge remains. Some strategies such as intraoperative monitoring, awake surgery, and intraoperative histology (margin biopsy) can be used to improve the goal. In this chapter neuronavigation, intraoperative magnet resonance imaging (ioMRI), and 5-aminolevulinic acid (5-ALA) are discussed as tools to improve the safety and efficacy of intracranial tumor resection.

2. Neuronavigation

Neuronavigation has a fundamental role in contemporary neurosurgery. This tool allowed surgeons to better individualize treatment tailoring craniotomies and localizing structures or lesions intraoperatively. It consists of a frameless stereotactic system of localization based on pre- or intraoperative image data. The data used can be a fusion of different techniques like CT, MRI anatomical or functional sequences, US, or PET-CT.

The most important indications of the use of navigation are planning of craniotomy, intraoperative localization of lesions or structures, and guided biopsies.

2.1 Craniotomy planning

Using metastasis as an example, neurosurgeons increasingly attempt to resect as much tumor tissue as possible to impact disease control and survival. If a patient has four metastases of 4 centimeters that can be completely resected, this procedure should be indicated. Even if multiple craniotomies are needed, this should not dissuade the surgeon to indicate it [1]. In these special cases, considering that these metastases are in different places of the brain, neuronavigation makes a real difference with a tailored and focused approach to each lesion.

Neuronavigation allows direct access to the lesions, even if small, reducing the size of craniotomy, dural opening, unwanted manipulation of the brain, duration of surgery, blood loss, volume of the tissue to be healed, length of stay in the hospital, recurrence rate, time to be available for complementary treatment if needed, and costs and improving recurrence-free survival (RFS) and performance status [2, 3].

In cases of ventricular endoscopic approach, neuronavigation can also be very useful. Some patients with pineal or third ventricle-located tumors with noncommunicating hydrocephalus, for example, need third ventriculostomy and biopsy. In order to offer a direct straightforward approach, avoiding lesions of related structures, two different trepanations/small craniotomies can be performed guided by neuronavigation (**Figure 1**).

Besides defining the position of the craniotomy, still regarding surgical approach, neuronavigation can help in many ways to improve safety of neurosurgical procedures. Identification of sinus position in retrosigmoid craniotomy has been demonstrated successfully avoiding unnecessary sinus exposition reducing complications [4]. Also, superficial vein identification before dural opening was demonstrated, eliminating the need to use indocyanine to make a transdural analysis, for

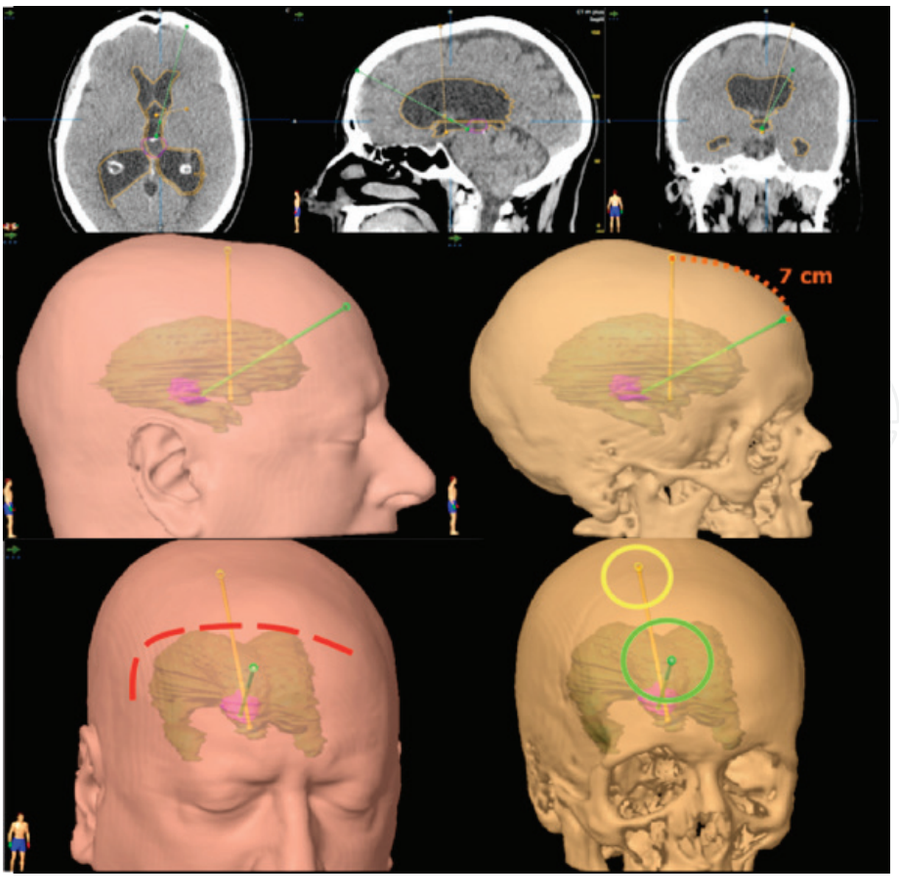


Figure 1.
Patient with indication of a third ventricle lesion and third ventriculostomy. Neuronavigation plan of two different craniotomies to straightforward approach avoiding critical structures. The yellow trajectory with direct approach to Monro's foramen and Liliequist membrane. The green target to direct approach of a third ventricle lesion. Approaches point distant 7 cm. Two small craniotomies were preferred and successfully achieved their targets.

example [5]. These strategies reduce also the risk of bleeding and venous closure, which can have a negative impact on surgical outcome.

2.2 Intraoperative localization of structures/lesions

When used to localize superficial lesions/anatomical structures and tailor surgical approach, neuronavigation has high accuracy, being a very reliable tool, because the intracranial compartment remains untouched. However, the main drawback of neuronavigation is that it is not a real-time evaluation.

The accuracy between preoperative images and real intraoperative anatomy is influenced during many surgical steps that result in dislocation of structures, called brain shift. Several surgical aspects are not related to wrong landmark selection, hardware movement, or software algorithm influence on brain shift. The causes are classified as physical (hardware movement, patient position, and gravity), surgical (fluid loss, tissue loss, and surgical equipment), and biological (mannitol and tumor type) [6].

The effect of gravity is an important physical factor of brain shift. It interacts with two surgical causes: fluid loss and tissue loss. After tumor resection or relevant CSF drainage, adjacent healthy tissue becomes unsupported with sagging of the brain. Loss of 20 cm^3 of CSF in deep brain stimulation (DBS) surgery was demonstrated to result in the shift of the anterior commissure by approximately 2 mm [7]. Mannitol administration during surgery also can influence, especially in cases

where high intracranial pressure levels or large edema are present. Neuronavigation does not contraindicate the administration of mannitol. But its use should be used judiciously, not routinely. Regarding biological causes, some authors observed an association between tumor biology and unique patterns of the shift. But the reasons are not well understood, and more studies should analyze this before generalization can be made [6].

Previously, many attempts to identify intra-axial tumor margins using neuronavigation were performed, but it could be done with reliable results due to brain shift. Other options such as fluorescence and ioMRI have superior results. Otherwise, targets located in fixed structures like the bone, brainstem, and skull base meninges tolerate better intracranial manipulation. The dural implantation of a skull base meningioma, for example, can be checked with navigation during the procedure, because it will suffer few the effect of brain shift. But as accuracy should be low, the shift needs to be weighted in every procedure. In brainstem biopsies, the passage of the biopsy needle through the parenchyma does not change target position significantly; but if the trajectory accidentally passes through the ventricle with CSF drainage, the brain shift can have significant influence hindering correct target achievement.

Correction of brain shift can be done using intraoperative MRI to update the navigation; or other real-time exams, where ioMRI is not available, can be performed to compare and adjust it such as ultrasound (US) [2, 8].

Ultrasound is a fast, cheap, real-time, and commonly available exam. Although its image quality is not comparable to MRI, it plays an important role in brain tumor surgery. After craniotomy, for example, brain shift can occur even if brain deformation is still not present. Placing the probe directly on the dura and superimposing identifiable structures on both techniques can confirm if neuronavigation is still adequate. The main concept of using intraoperative US is that the focus is not on diagnosis but on localization. Undoubtedly, MRI is the gold standard exam to analyze brain lesions and define diagnosis. But to locate lesions and some structures, US is sometimes enough with the advantage of being easily and real-time performed. ioUS can affect the decision of further resection in 59% of cases [9]. Association of these two techniques offers the possibility to overcome the limitations of each one separately improving the safety of the procedure (**Figure 2**).

Another important intraoperative use of navigation is in the association with other tools such as awake surgery and transcranial magnetic stimulation (TMS). Navigated TMS-based DTI-fiber tracking in awake surgery has been demonstrated

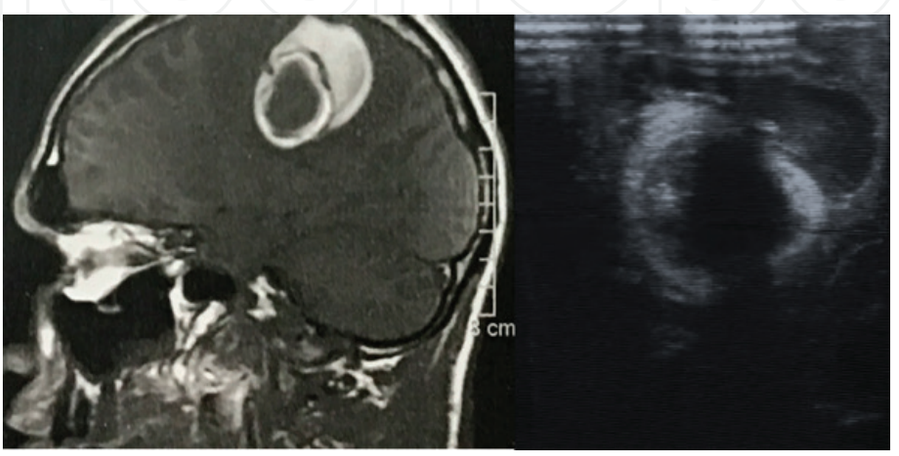


Figure 2.
MRI of a hemorrhagic tumor with ioUS view. Easy identification of both limits and differences of cystic and solid components.

as a useful tool in the treatment of highly eloquent gliomas with results considering craniotomy size, EOR, duration of surgery, postoperative deficits, Karnofsky Performance Scale (KPS), and length of stay in the hospital [10]. Association of image-guided resection of glioblastoma in eloquent brain areas facilitated by laser surface thermal therapy was also demonstrated with favorable long-term results. This strategy allowed the higher rates of complete resection and improved overall survival without the negative effect on postoperative functional status [11].

2.3 Guided biopsy

Biopsy of intracranial lesion is an important diagnostic tool in neurosurgery. With the progression of genetic and molecular characterization of tumors, biopsy becomes even more important in deep-seated lesions with difficult access such as in the thalamus, brainstem, and pineal gland.

Frame-based intracranial biopsy has been the gold standard technique for intracranial biopsy for a long time. The stereotactic system provides excellent precision of target achievement. After development of neuronavigation, the frameless intracranial biopsy, guided by neurosurgery, has evolved a lot. Both methods have similar effectiveness to histological diagnosis. But a frameless system has become increasingly the first choice among neurosurgeons due to reduced equipment size; reduced work of calculations to define targets, entry point, and trajectory; patient's comfort; reduced surgical time with navigation; and the absence of the need to redo image examination after placement of the frame (**Figure 3**) [12].

The use of real-time ioMRI-guided biopsy has also been compared to frame-based and frameless neuronavigation-guided biopsy with comparable diagnostic yield in patients with no prior treatment. ioMRI-guided biopsy was associated with short hospital stay [12]. But ioMRI is not available in many places, and navigation-guided frameless biopsy continues as the first option in most departments.

In pineal tumors, as some patients have hydrocephalus, endoscopic biopsy associated with third ventriculostomy is a feasible option, as cited before.

The most common complications of deep biopsies are brain shift, hemorrhage, and failure in representativeness of samples. Brain shift was discussed before in Section 2.2. Hemorrhage can be directly related to biopsy (intratumoral) or to the trajectory

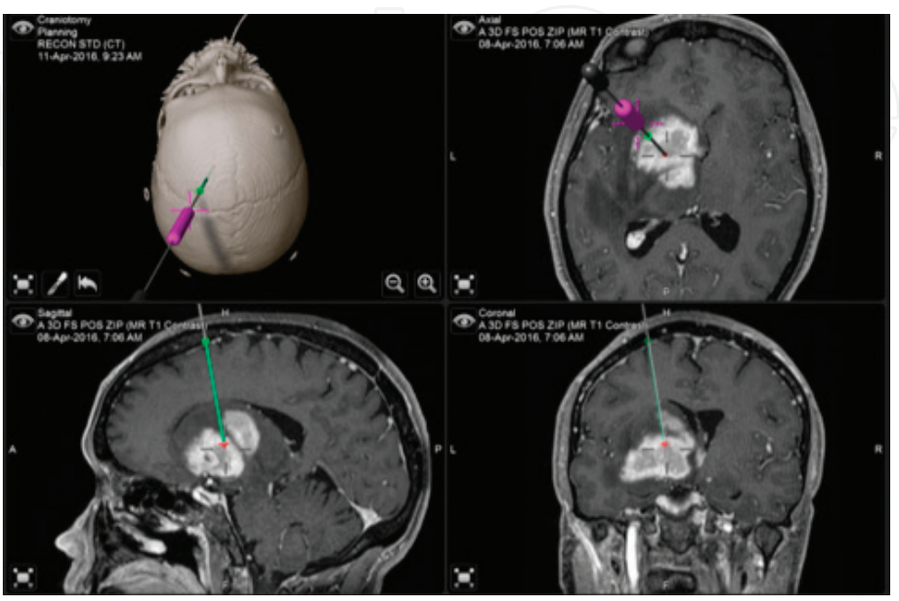


Figure 3.
MRI of a frameless-based biopsy (neuronavigation guided) of a deep-seated lesion. Trajectory planning without any passage through ventricular system to avoid CSF drainage and brain shift.

(needle track). Hemorrhage is avoided with preoperative evaluation of coagulation marking a trajectory that avoids any arterial or venous structure that is achieved by using multiplanar reconstruction of image [13]. Representativeness of sample has been traditionally analyzed with adequate target definition in image and intraoperative pathology/frozen section. More recently fluorescence has been associated with biopsy procedures with good correlation compared to frozen section to check acquisition of relevant samples. Both 5-ALA and fluorescein were evaluated [14, 15].

3. Magnet resonance imaging (MRI)

In neuro-oncological surgery, complete resection with preservation of functions and quality of life is normally the goal of the procedure. Defining complete resection intraoperatively is easier in extra-axial tumors than in intra-axial tumors such as low-grade gliomas. A surgeon's perception of gross total resection (GTR) usually relies on the visual and tactile aspects of tumor boundaries. Studies compared the surgeon's perception with imaging findings and determined inaccuracy and overestimation of intraoperative EOR by up to a factor of 3 [16–18]. Young adult patients with low-grade glioma who undergo a neurosurgeon-determined GTR have a higher than 50% risk of tumor progression in 5 years postoperatively [18].

The surgeon's experience also was not significant to define additional resection. The positive predictive value (PPV) of the surgeon's expectation was shown to be high (93.1%). On the other hand, and most importantly, the ability to exclude additional resection from the intraoperative impression was very low (43.6%) [19].

This is a major concern specially in tumors that EOR is proven to be related with recurrence and survival.

Intraoperative or transoperative MRI emerges exactly in this context to clearly determine if GTR was achieved or not. Literature suggests rates of further operative resection secondary to ioMRI evaluation range from 13.3 to 59.37%, confirming the impact of this tool on the extent of tumor resection [20, 21].

Analysis comparing EOR, GTR, and progression-free survival (PFS) and overall survival (OS) in patients with gliomas that underwent ioMRI also confirmed the benefit with improvement of these aspects. The author showed an increase in GTR rate of 24.1%. In 59.37% of cases that underwent ioMRI, further resection was needed [21]. Certainty of ioMRI can make surgeon more tolerant and relaxed, ending resection early relying on ioMRI evaluation. But even if this is considered, the improve in resection is substantial.

In complex located tumors, for example, insular gliomas, ioMRI check during awake craniotomy increased EOR in 15.1%. Considering that median EOR on ioMRI was 51.2% and after further resection was 84.5%, it is clear that ioMRI really impacts outcome [22].

Identification of margins is not always simple. It depends on the tumor type, MRI sequence analyzed, and surgical trauma with blood-brain barrier break. In cases of high-grade glioma surgery, PWI helps in identification of tumoral x non-tumoral tissue. Another option is the use of a single layer of oxidized regenerated cellulose covering the cavity to enhance margin visualization in ioMRI. Being a hemostatic agent, it accelerates oxidation of oxyhemoglobin to metahemoglobin, which is paramagnetic, and, so, it has a hyperintense signal in T1 sequences. This layer of hyperintense line observed may be a useful marker of tumor resection borders in cerebral glioma surgery [23].

Pituitary tumors also benefit from ioMRI. A systematic review observed that complete radiological resection in patients whose procedure involved intraoperative ultrasound was 67.1% (range 63.5–77.8%) and endocrine remission was 88.4% (range

76–100%) [24]. Studies with ioMRI also evidences the benefits with intraoperative unexpected residuals in up to 42% (range 15–83%) of cases, of which re-exploration was attempted in 36% (range 9–83%) and further tumor resection occurred in 33% (range 9–83%) of the cases [25]. But this paper considered low- and high-field ioMRI. In a study with 3 T ioMR, a complete resection was observed in 69% of the cases.

Intraoperative image interpretation is even more difficult in transsphenoidal pituitary surgery than in glioma surgery, for example. This evaluation should only be done by an experienced neuroradiologist, because the literature shows relevant cases of false-positive leading to resection of normal tissue, in both ioMRI and ioUS [24, 25]. The Congress of Neurological Surgeons (CNS) suggested in 2016 that intraoperative images in nonfunctioning adenomas may help to improve overall gross total resection but at the cost of removing normal tissue [26]. So, we suggest weighting cost-benefit relation differently in nonfunctioning x functioning adenomas. But in an experienced team, good results can be achieved.

In the beginning, ioMRI started with low-field strengths of 0.2–0.5 T. These units, although cheaper and requiring less spaces, take longer to perform scanning and produce low-quality images when compared to high-field (1.5 T and higher) equipment. Besides this, the possibility of advanced images such as DTI favors the use of high-field equipment [27, 28].

Cost is one of the most limiting factors to the spread of ioMRI. Additionally, the price of the whole equipment and software and surgical and anesthesia equipment should be developed to be compatible with ioMRI environment. These adapted equipment are also expensive, which increases even more the investment on a magnet dedicated exclusively to intraoperative images. Besides this, in few years MRI equipment becomes obsolete with the need to change to maintain it updated.

In order to overcome this limitation, the concept of "outside MRI" was proposed by Ramina et al. in 2010. In this strategy after completing the resection, oxidized regenerated cellulose is put to cover surgical cavity, and a partial closure of the dura is performed. The exposed dura is covered with cottonoid plates, and the skin is closed with running suture. A sterile plastic sheet covers the entire head to assure sterility and complete the preparation for MRI. The patient is conducted in the MRI-compatible bed through an internal special lift, designed for this purpose, to the MRI facilities. Time required to whole exam, since patient left OR and came back, was 25 min. No infection was observed [29]. Ahmadi et al. recently confirmed that inside ioMRI did not increase complications (hemorrhage, wound healing, and infection) in glioma surgery. In their publication the ioMRI procedure time was higher with a mean of 57 min [30]. "Outside MRI" has all advantages of "inside models" and the additional advantage of integrating neurosurgery/neuroradiology teams, which may lead to better results [29].

4. 5-Aminolevulinic acid

5-ALA is a prodrug and leads to accumulation of protoporphyrin IX (PPIX) in gliomas and other tumor cells by an interaction with heme biosynthesis process. With special filters and blue/violet light, it is possible to see fluorescence of PPIX as light red or an intense pinkish color in a dark blue background. These filters and lights are usually part or an upgrade of surgical microscope. Normal brain tissue does not induce PPIX expression after ALA administration, and a high selectivity of malignant glioma cells is observed. When density of tumor cells in the tissue is above 10%, fluorescence is expected to be present [31].

This is another tool to go further with the concept that tumor tissues are many times much more than what we see with normal light surgical microscopy or even contrast-enhanced MRI. A high association between contrast enhancement and PPIX fluorescence is observed. But it was shown that PPIX fluorescence in non-contrast-enhanced areas can be present with good correlation with the presence of tumor tissue. So, PPIX accumulations seem to be more sensitive to glioma detection than contrast-agent accumulation (**Figure 4**) [31, 32].

Fluoroethyl tyrosine PET has been demonstrated to have a good correlation with PPIX fluorescence in gliomas without typical glioblastoma imaging features [33]. Also, areas with high atypia in low grade or non-contrast enhancing in high grade suggested by PET could be confirmed with 5-ALA fluorescence. The explanation to these findings may be in the mechanism of each method. Contrast enhancement and sodium-fluorescein fluorescence have intraoperative correlation, and both occur due to disruption of blood-brain barrier, which is not specific from tumors. 5-ALA fluorescence and PET tracer uptake, in turn, occur due to specific metabolism of tumor tissue. 5-ALA may be even more special than PET because it does not consider only the general quantitative aspect of metabolism and goes beyond. Its mechanism relates to a metabolic phenomenon of a pathway typical from a tumor tissue and not from a normal tissue [34].

Other tumors than WHO IV gliomas have also been tested regarding fluorescence after 5-ALA administration. Literature shows results with approximately 15–20% of fluorescence with 5-ALA in low-grade gliomas, 85–100% in high-grade gliomas, and 55–80% in metastasis [32, 35, 36]. In our most recent data analysis from INC, we could observe 5-ALA-positive fluorescence in 97.7% cases of WHO IV gliomas, 90% cases of WHO III gliomas, 22.2% cases of WHO II gliomas, and 85.7% in cases of metastasis. The quality of fluorescence differs among tumor types. In low-grade gliomas, for example, with positive fluorescence we observed usually weak to mild with stronger foci in some cases (higher atypia); metastasis, on the other hand, usually shows mild to strong fluorescence (**Figure 5**).

During the procedure, the surgeon alternates between white light resection and blue/violet light resection. This is important because white light shows anatomy, structures, and blood better. Only the resection, specially boundaries, is guided by fluorescence. Blood, inclusive, may be a confounding factor, because it prevents the

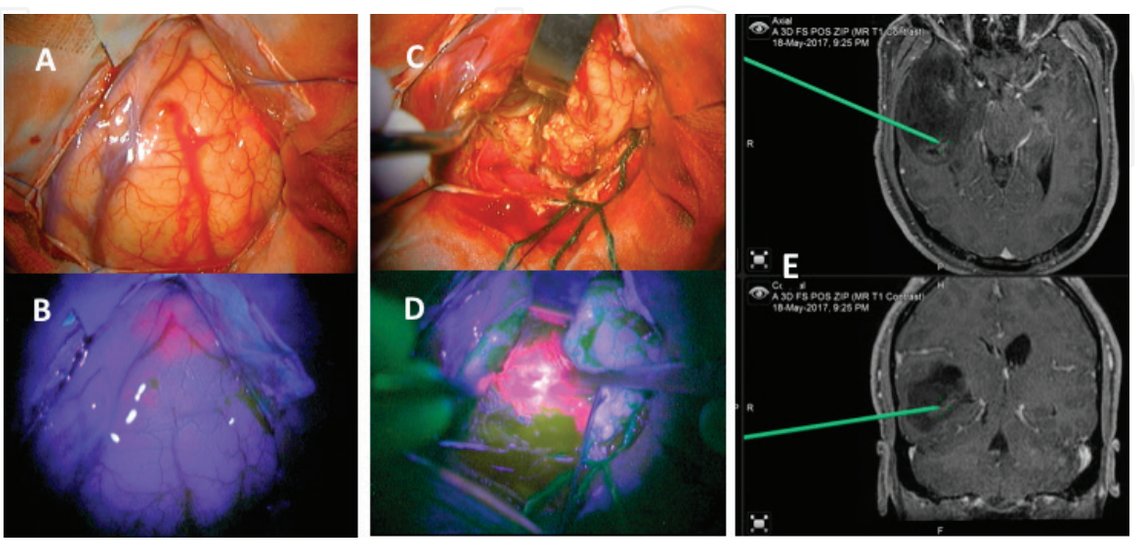


Figure 4.
Glioma patient operated on using 5-ALA. A and B show white light and blue-filter images with identifiable tumoral tissue on the cortex, clearly visible with blue filter and difficult to identify with white light. C and D show areas of tumor with intense fluorescence in blue filter, corresponding to contrast-enhanced area shown by neuronavigation in E.

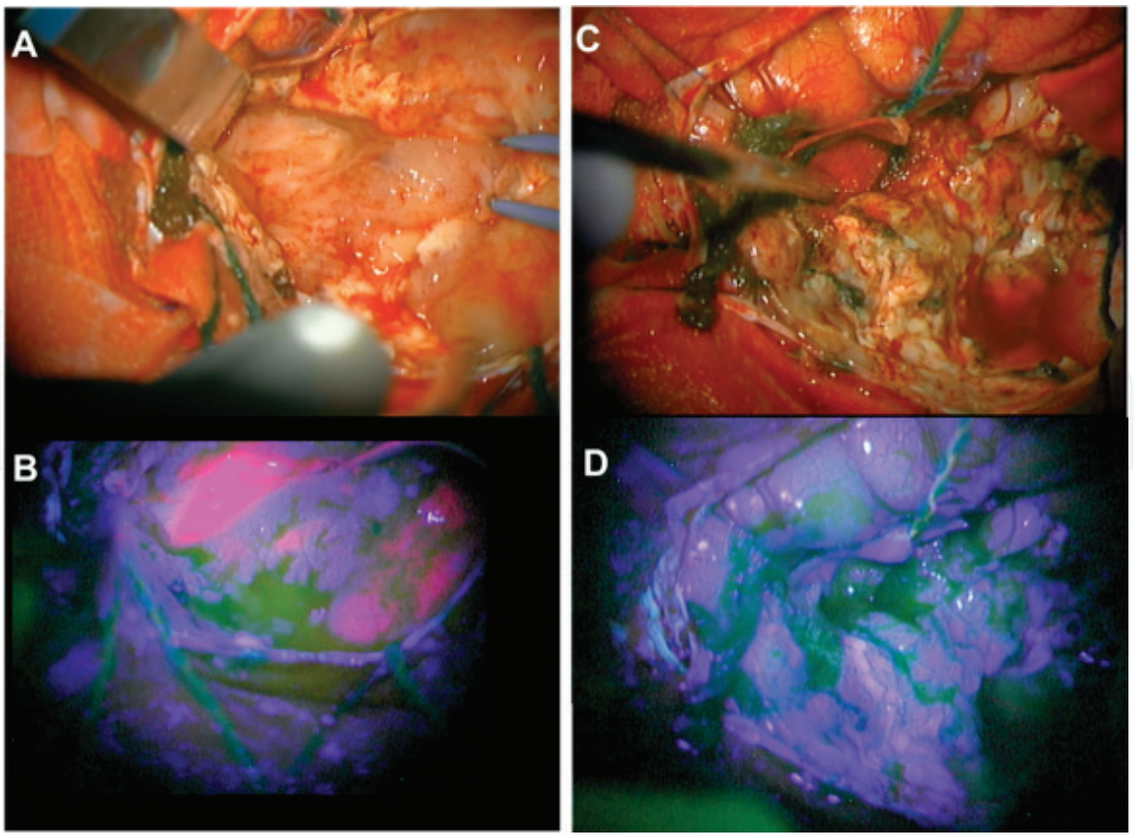


Figure 5.
High-grade glioma patient operated on using 5-ALA. A and B show white light and blue-filter images with clearly identifiable tumoral tissue. In blue-filter image, a reddish color is observed, confirming the presence of tumoral tissue. The pinkish image demonstrates areas with tumoral infiltration. C and D show complete resection without any identifiable tumor in both white light and blue-filter images. Normal tissue appears blueish.

visualization of fluorescence. So, an adequate size of craniotomy (allowing light to enter the deep surgical field) and hemostasis (to avoid a blood layer over tumor area) in 5-ALA-guided surgery are more than ever must-do concepts. More common collateral effects are transient increase in liver enzymes and light sensitivity of the skin until 24 h after administration.

A combination of techniques may be the future of fluorescence-guided surgery. Dual-labeling surgery using 5-ALA and fluorescein has been tested with interesting results. Fluorescein created a useful background for 5-ALA fluorescence. It appeared as orange to red surrounded by greenly fluorescent normal brain and edematous tissue. Unspecific extravasation of fluorescein at resection margins was also observed, which did not interfere with 5-ALA fluorescence detection [37].

EOR and 6-month PFS have been proven to increase with the use of 5-ALA in cases of malignant gliomas. PFS at 6 months was 41% in 5-ALA group x 21.1% in the group operated only with white light-based resection. EOR improved from 36% in white light-based resection to 65% in 5-ALA [38]. EOR has also been analyzed in a systematic review with 22 series from the literature, including 1163 patients, with a GTR rate of 66.2% in gliomas using 5-ALA [35].

Other non-fluorescence techniques can also help in combination with 5-ALA. Intraoperative cortical stimulation added new advantages to resection about the function of tissues and provided additional safety for resection of primary malignant tumor in eloquent areas [39]. Intraoperative 3D US, as well as ioMRI, also was demonstrated to bring different information that when combined with 5-ALA fluorescence can improve the extent of resection, especially in non-enhancing tumors [9, 31, 40].

A comparison of combined ioMRI + 5-ALA versus ioMRI isolated in patients with high grade (WHO IV) gliomas showed that in combined group EOR above 95% was reached in all cases. In the ioMRI group, 18% of EOR were below 95% with a minimum EOR of 87% in this group versus a minimum EOR of 97% in the combined group [40]. Considering that EOR of 78% is the cutoff to improve survival in high-grade gliomas, both methods were efficient. But the association of 5-ALA and ioMRI leads to a higher rate, possibly having a greater impact on survival. But this is still to be proven, demanding further studies.

Despite drawbacks of being only a 2D information, hidden 5-ALA fluorescence by blood or hemostatic agents, and regulatory issues in many countries, 5-ALA-guided resection is a very useful tool offering real-time information from the tissue (not indirectly not from images), without the influence of brain shift avoiding second-look procedures or even new complementary resections, which are usually much more expensive than the costs of 5-ALA (**Figure 5**).

5. Conclusion

Every tool that can add data to surgical planning or intraoperative evaluation is valid. Neuronavigation is very useful in surgical strategy (planning and intraoperative steps) improving efficacy and safety of the procedure. 5-ALA-guided resection and intraoperative image (such as ioUS and ioMRI) are proven to be cost-effective with increased GTR rates and an impact on survival. The future probably will prove that combination of these tools, selected case by case, is the best way to achieve the best results regarding safety and effectiveness.

Conflict of interest

Authors have no conflict of interest.

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