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# Multimodal Neuronavigation for Brain Tumor Surgery

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## Abstract

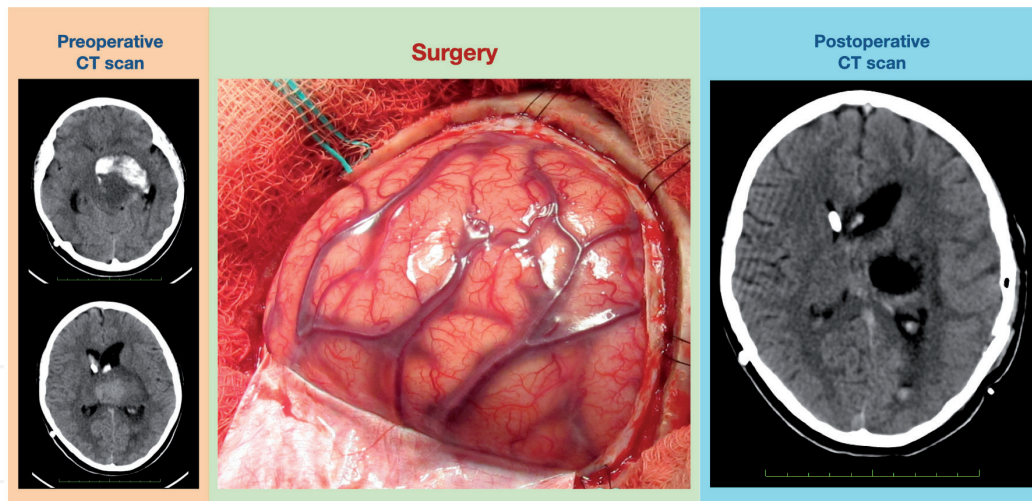
The current neuronavigation techniques increase safety and surgeon confidence during neurosurgical procedure performance. However, its real usefulness remains in integrating multimodal information from advanced magnetic resonance imaging, as tractography (DTI), functional studies that evaluate motor and sensitive language, motor function (BOLD techniques with different paradigms), and nuclear medicine. At the operating room, the fusion of sonographic information acquired in real-time with the predefined plan increase the chance to achieve gross-total resection of primary brain tumors. Combining these different image modalities with brain mapping and motor stimulation information in selected cases is possible, increasing surgery safety. In this review, we present our experience with multimodal neuronavigation to treat brain tumors in pediatric patients.

**Keywords:** Neuronavigation, fMRI, BOLD, PET/CT, Brain tumor, Cancer

## 1. Introduction

Gliomas are primary tumors of the central nervous system. They are derived from glial cells. They are the most common cause of solid tumors in the intracranial space in children [1]. Nearly 70,000 new cases of malignant primary and benign brain tumors of the central nervous system (CNS) are diagnosed in the United States each year. Of these, approximately 28% are gliomas, and 36% are meningiomas. Gliomas represent 80% of the primary malignant brain tumors. The incidence rates of brain tumors have increased in the last three decades. For all CNS tumors, of which brain tumors account for approximately 88%, the average annual incidence rate adjusted for age (2006 to 2010) for women (22.8 per 100,000) is higher than for men (19.1 per 100,000) [1, 2].

According to the World Health Organization (WHO) classification of brain tumors, they are divided into gliomas of the low and high degree of malignancy. Low-grade gliomas - I and II, are represented by pilocytic astrocytoma, diffuse glioma, and gemistocytic astrocytoma. They have a benign clinical course with a long survival time. High-grade gliomas, anaplastic astrocytoma (grade III) and glioblastoma multiforme (grade IV), are characterized by a rapid growth rate,



**Figure 1.** *Intraoperative cerebral edema during emergency surgery in a patient with neurological deterioration secondary to a brain tumor bleeding.*

extensive white matter infiltration, and poor short-term prognosis [3, 4]. Therefore, the histopathological diagnosis and its proper classification are crucial for treating patients. Diffuse astrocytoma (WHO grade II) is characterized by slow growth and infiltration of neighboring brain structures **Figure 1** [5–7].

In pediatric patients, the central nervous system's tumors represent the second cause of cancer mortality after leukemia. The magnetic resonance imaging technique renders the integration of different structural images (FLAIR, diffusion, perfusion, SPGR, TRUFFI), functional aspects (DTI, BOLD), and metabolic profile (spectroscopy). They evaluated peritumoral edema by diffusion and perfusion sequences [8, 9]. The use of sequences that provide functional information allows the early identification of the risks associated with neurosurgical treatment and each case's functional prognosis [10]. Some reports show a characteristic uptake pattern for the degree of malignancy of different neoplasms. In the case of primary tumors of the CNS, significant alterations can be observed in the uptake of glucose, methionine, and tyrosine. One of the technological resources that have changed the treatment of patients with CNS neoplasms is neuronavigation.

## 2. Characteristics of Magnetic Resonance Imaging Studies for Neuronavigation

The radiological evaluation of brain tumors makes it possible to identify the structural, functional, and metabolic characteristics of neoplastic lesions and, for prognostic purposes, their relationship with healthy brain tissue by combining diverse image acquisition techniques.

The MRI imaging modalities currently used in presurgical planning for brain tumor resection are functional magnetic resonance imaging (fMRI), diffusion tensor (DTI) imaging, diffusion tensor tractography, and BOLD [2].

### 2.1 Diffusion Tensor Images (DTI)

The diffusion tensor images allow the visualization and characterization of white matter tracts [11–13]. DTI images have been used to study the architecture of white matter and the integrity of normal and diseased brains. This magnetic resonance technique is based on the general principle that the anatomical microstructure directs water diffusion, being an echo-planar technique that maps the diffusion

speed [14]. In brain tissue, diffusion rates are slower due to the typical parenchyma components that impede water movement. In specific pathological processes, water diffusion is restricted, which reduces the apparent diffusion coefficient (ADC), as in acute infarcts secondary to cytotoxic edema, abscess, lymphoma [12, 15]. Fiber tracking is the only non-invasive method to visualize the course, displacement, or interruption of white matter's main tracts according to the DTI technique. Multiple studies have shown that fiber tracking can reconstruct white matter's major fiber structures in the brain. Identifying the tracts is done by defining a rectangular interest volume (VOI) in the registered standard T1 anatomical datasets. A fast acquisition gradient echo sequence prepared with 3D magnetization weighted in T1 is used to acquire the images. T2-weighted images are acquired, inversion recovery images attenuated by T2 fluid, and 3D images weighted in T1 postcontrast are scanned. Intraoperative examinations are performed immediately when the operator considers that the lesion has been resected or intraoperative exploration was necessary to correct the cerebral displacement. For DTI, applies a sequence of echo-planar images weighted by spin-echo diffusion of a single shot (echo time, 147 milliseconds, repetition time, 9400 milliseconds, matrix size,  $128 \times 128$ , the field of view,  $251 \times 251$  mm, the thickness of cut, 3 mm, bandwidth, 1502 Hz per pixel, diffusion encoding gradients in 12 directions with b values of 0 and  $1000 \text{ s/mm}^2$ , and voxel size,  $1.9 \times 1.9 \times 3$  mm) [12, 13, 16]. The 3D segmental reconstruction of the tumor is performed based on the high-resolution 3D postcontrast anatomical data set.

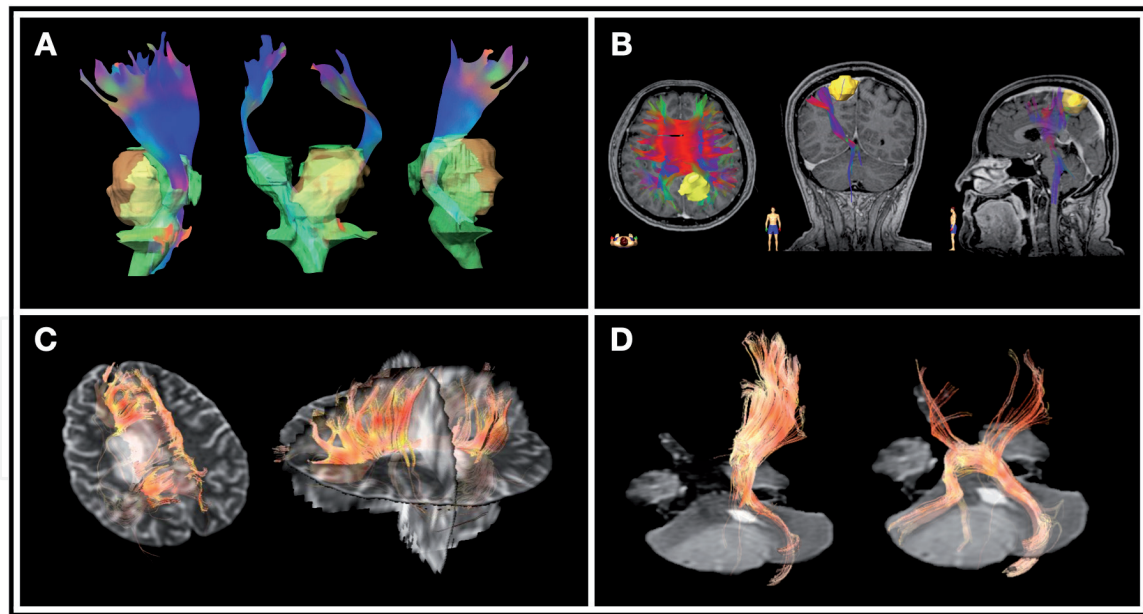
In the case of tumors with high uptake of contrast medium - glioblastoma multiforme, metastasis, the edge of the outermost lesion that enhances post-contrast, for example, glioblastoma, and the edge of hyperintensity or mixed hypointensity in the lesion, such as the non-malignant entity, cavernoma, represented the limit of segmentation. In non-enhancing lesions such as low-grade glioma, the T2-weighted image is used to determine the tumor's edge. For this reason, most tumors that do not have post-contrast enhancement have optimal visibility in this sequence. The existence of significant edema, which cannot be clearly distinguished from the low-grade glioma, was ruled out based on the findings of inversion recovery images with T2 fluid. The segmentation of the tumor is performed by cutting in a mode of 3D anatomical data. After profiling all the sections that contained the lesion, the three-dimensional reconstruction of the lesion was performed [13].

The techniques of DTI and tractography have overcome this obstacle and are now widely used to study the white matter in vivo. Diffusion images calculate the local direction of white matter from water diffusion measurements. Tractography takes this a step further to evaluate the functional connection between several different areas inside the same or contralateral hemisphere. The identification of water molecule's movement in all directions is known as isotropic diffusion. In the central nervous system, anisotropic diffusion is used to define water's movement in a parallel sense in the white matter tracts defined by axons' groups. Thus, creating maps of movement of water that define the structure and orientation of white matter tracts [2, 3].

Three-dimensional visualization of white substance fibers, such as the corticospinal (pyramidal) tract, corpus callosum, cerebellar peduncles, optical radiation, and arcuate fascicle, is of great value at the preoperative evaluation and intraoperative navigation **Figure 2** [4].

## 2.2 Perfusion

There are three main techniques for perfusion imaging: T2\* enhanced dynamic magnetic susceptibility enhanced perfusion in T1-enhanced dynamic contrast, and arterial spin marking techniques, involving repetitive serial images through the tumor during blood passage been marked with contrast material.



**Figure 2.**

*3D reconstructions for white matter tracts with DTI-MRI technique. (A) Thalamic high-grade glioma and his relationship with the pyramidal tract. (B) Parasagittal meningioma and its relationship with corpus callosum and pyramidal tract. (C) Supratentorial Ependymoma and its relations with Corpus callosum. (D) Fourth ventricle tumor and middle cerebellar peduncle displacement.*

Theoretically, the degree of a signal drop is proportional to the concentration of gadolinium in the tissue, obtaining relative curves of concentration - time. Dynamic contrast images weighted in T1, where the main focus is estimating tumor permeability, allow the contrast to filter into the extravascular space and reach equilibrium during multiple contrast bolus passes through the tumor bed. An arterial spin is a form of perfusion without the use of intravenous contrast; a powerful magnetic gradient is applied to the blood inlet to reverse the magnetization, effectively labeling the blood that flows upward, have impeded its application for long periods of imaging and decrease in spatial resolution compared to gadolinium [16]. Different types of tumors and grades differ in their perfusion characteristics. For example, there is a strong correlation between the degree of astrocytoma and the relative measurements of cerebral blood volume (CBV) [17]. However, low-grade astrocytomas tend to have a high cerebral blood volume, associated with the process of angiogenesis and dense capillary networks that characterize these tumors.

### 2.3 Magnetic resonance spectroscopy

It provides an analysis of the different metabolites in a delimited area within the brain and may be useful in the initial diagnosis of brain tumors. It can be done with a single voxel technique, in which a single spectrum is produced for a tissue volume, or a multivoxel technique, in which a greater volume of tissue is evaluated [18]. The primary metabolites evaluated include N-acetyl aspartate (NAA) (typical neuronal marker), choline (cell membrane marker), creatine (energy marker), lactate (metabolic acidosis), and lipids (tissue breakdown and cell death). The spectral patterns of intracranial neoplasms vary significantly due to differences in tumor types and grades. However, most CNS tumors manifest with elevated choline-creatine and co-NAA ratios caused by increases in cellularity (choline elevation) and a relative decrease in normal neurons (reduction of NAA).

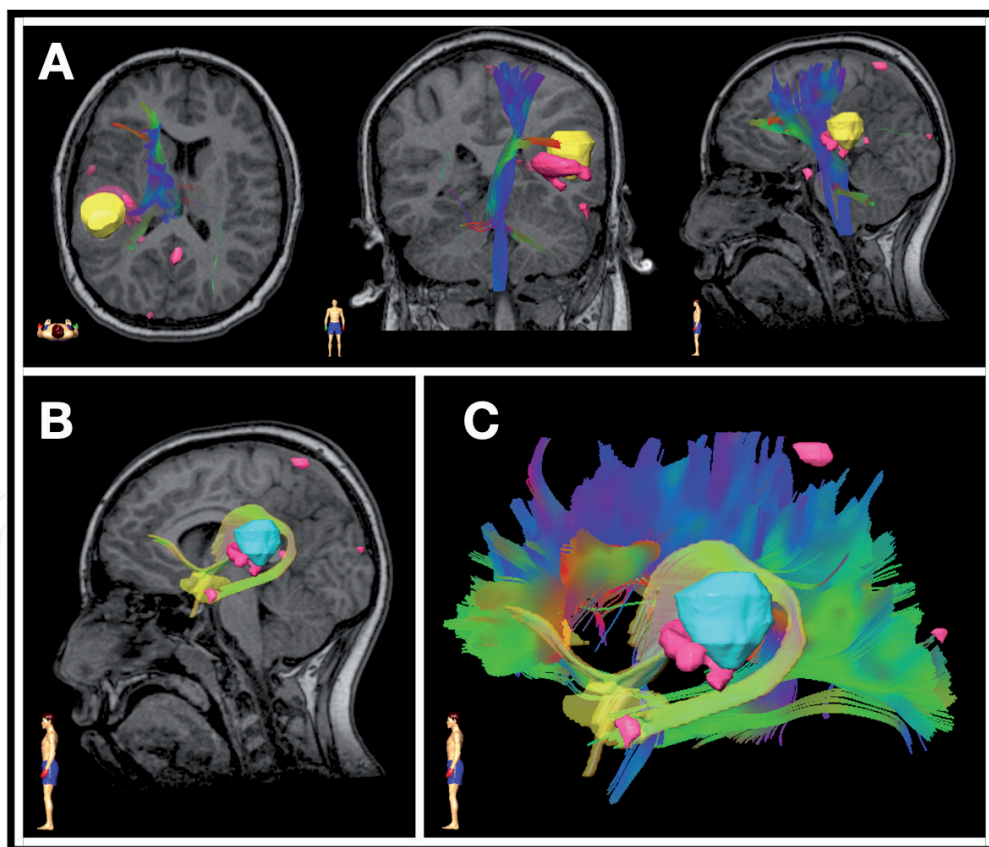
## 2.4 Functional MRI Images

Functional MRI (fMRI) mapping of eloquent language cortex in patients with brain tumors after surgery is feasible and may serve as a useful reference assessment for preoperative neurosurgical planning [19].

Functional magnetic resonance imaging (MR) is an advanced tool for studying brain functions in healthy subjects and neuropsychiatric patients, identifying and locating specific metabolism and neural activity phenomena [20].

BOLD is a measure of changes in oxygenated and deoxygenated blood proportion during a particular paradigm's execution. The most commonly mapped functions during functional MRI studies include motor, auditory, somatosensory, visual perception, and language production and comprehension. When evaluating motor centers, typical tasks include tapping with fingers, pouting with lips, and flexing and extending toes [21]. Patients with mild to severe motor paresis of the hand may clench their fists instead of tapping with their fingers.

Several reports mention that a silent area around a brain tumor could recover his eloquence after the surgical resection of malignant tissue [22]. There is a latency of several seconds in the signal change observed in BOLD images, making the temporal resolution of functional MRI poor compared to other techniques such as DES or electroencephalography [23]. Because of the “delay of hemodynamic response” given the time required for the production and diffusion of vascular signal



**Figure 3.**

*The utility of fMRI and tractography for surgical planning. An 8-years-old boy presents at the emergency unit with a history of intermittent language disturbances and right-hemiparesis. fMRI (language paradigm) and DTI (Pyramidal tract, Corpus callous, Arcuate fascicle) images were performed. A 3D reconstruction at the Brainlab neuronavigation station was performed. (A) Pyramidal tract reconstruction and his relationship with a neoplastic lesion (Yellow) and language areas visualized with fMRI (Red). (B) Arcuate fascicle reconstruction and language areas and their relation to the neoplastic lesion. (C) 3D reconstruction of arcuate fascicle (Yellow), language areas (Red), and neoplastic lesion (Cyan).*

substances to dilate the vascular bed and cause a deoxygenated hemoglobin wash. Another consideration is that BOLD fMRI does not directly measure neural activity but changes in the region's hemodynamic properties. So, the variability between functional localization among subjects may result from physiological differences in the BOLD signal without differences in neuronal activity per se. It has been found that several pharmacological agents may influence the BOLD signal [24].

### 2.5 The utility of fMRI and DTI in presurgical planning

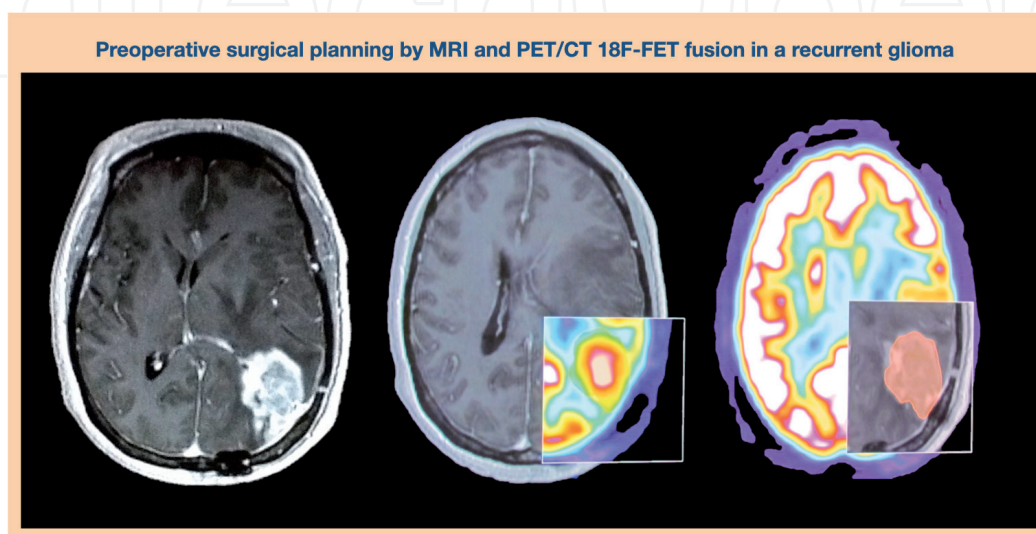
The use of fMRI in conjunction with DTI for presurgical planning is currently the most established clinical application of these neuroimaging techniques. The aim is to provide the surgeon with functional information about the tumor's area and its connections to adjacent areas. The regions of interest can be defined anatomically. However, the advance of functional imaging techniques allows us to define white matter tracts more precisely. Some reports mention that it is reliable in healthy ones but maybe inaccurate in those who harbor brain injuries **Figure 3** [21].

## 3. Nuclear medicine for imaging brain tumors

In Mexico, PET positron emission tomography equipment began with opening the PET-Cyclotron Unit of the National Autonomous University of Mexico in 2002. We use nuclear medicine to determine the degree of malignancy of the lesions, evaluate the response to treatment, identify early recurrence, and radiotherapy planning.

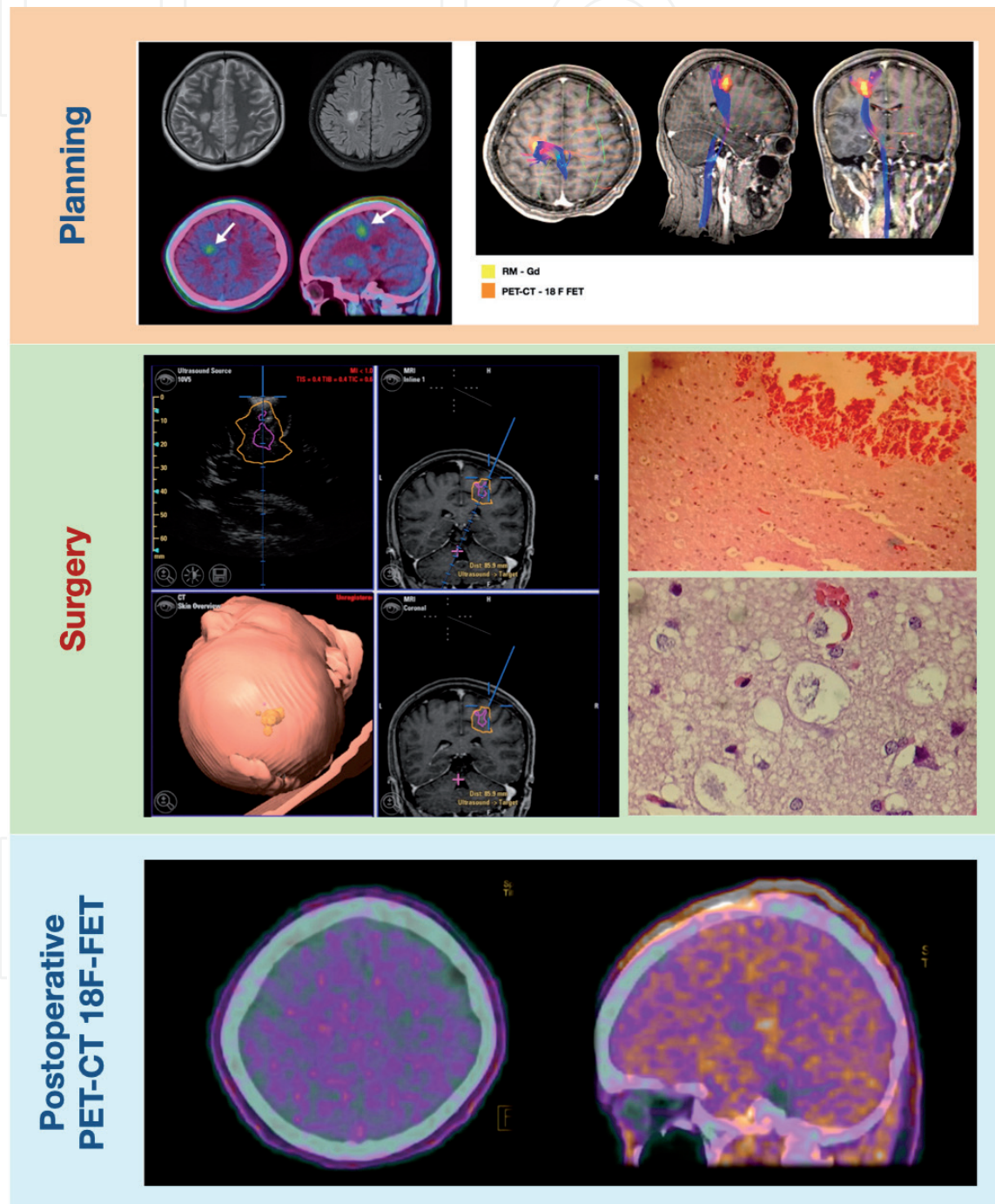
By obtaining functional information of cellular and biological processes like glucose metabolism, protein synthesis, the PET with 18 fluoro-deoxy-glucose (FDG) PET was initially used to detect and distinguish tumors of a low and high degree of malignancy. 18 Fluoro-ethyl-tyrosine (18 F FET) evaluates the metabolism of amino acids. It provides well-contrasted images in both high and low-grade tumors. It is beneficial to take biopsies guided by image to establish a primary brain tumor diagnosis in the planning of radiotherapy treatments and distinguish between tumor recurrence or radionecrosis after initial therapy **Figure 4** [4].

It has a sensitivity of 94% and specificity of 88% for the diagnosis of brain tumors. Although the 18-FDG and 18-FET quantitative parameters allow the



**Figure 4.**  
*MRI and PET/CT 18F-FET fusion for brain tumor recurrence resection.*

distinction between low and high-grade tumors, only the 18-F FET values can distinguish between tumor and non-tumor lesions, confirming the superiority of 18-F FET over 18-FDG for the characterization of brain lesions. Since 18-FDG is unreliable for predicting the neoplastic nature due to absorption by inflammatory lesions, amino acid tracers such as FET have been developed in recent decades to increase specificity. However, to date, only a few studies limited to small population of patients compared the diagnostic value of 18-FDG and 18-FET. Goldman and Pirotte thoroughly reviewed the clinical management, images, and PET role [25].



**Figure 5.** The utility of Multimodal Neuronavigation for brain tumor resection. A 15-years-old girl was received with a history of left hemiparesis and tonic-clonic seizures. MRI was performed, and a low-grade glioma was suspected. DTI sequences were obtained. A PET-CT 18F-FET was obtained, and fusion with structural and DTI images was performed at the Brainlab workstation. (A) Structural MRI, 18F-FET PET-CT, and DTI for pyramidal tract were fused during neuronavigation planning. (B) Right, Transoperative 3D ultrasonographic images were obtained and fused with the previous neuronavigational plan. Left, Histopathological analysis reveals a diffuse glioma. (C) At 48 months of follow-up, a new 18F-FET PET-CT was performed, no metabolic activity was detected.



On average, glioblastoma multiforme and medulloblastoma had a uniform and intense uptake throughout the tumor, while brainstem gliomas had a low uptake in less than 50% of the tumor and ependymoma had a low uptake throughout the tumor. When more than 50% of the tumor had uptake, the apparent diffusion coefficient was lower, which agrees with the increase in cellularity. In refractory/recurrent brain gliomas, the low correlation between uptake and enhancement is associated with decreased patient survival. It may reflect concurrent tissue degradation in the disease sites that received treatment and the development of new malignancy sites characterized by increased uptake of 18-F-FDG [26, 27].

The PET/MRI fusion tool in evaluating postoperative and radiooncological treatments provides information for tumor response, progression, and necrosis by radiation, affording the patients' oncological and functional prognosis **Figure 5**.

#### 4. Neuronavigation principles

Neuronavigation systems provide intraoperative guidance to the surgeon. Nevertheless, its real advantage is also to help them plan a proper surgical approach to avoid injury and incorporates functional data provided by preoperative images of magnetic resonance imaging, nuclear medicine, intraoperative sonographic studies, and in some places, magnetoencephalography (MEG) to prevent damage to eloquent areas during brain surgery [1].

Image-guided neuronavigation uses the principle of stereotaxy. The brain is considered a geometric entity divided into three imaginary spatial planes that intersect, orthogonal to each other (axial, coronal, and sagittal). Theoretically, any point within the brain is designated by a specific series of coordinates in each plane.

Neuronavigation platforms provide the unique opportunity to translate the two-dimensional information obtained from several imaging techniques – CT scan, MRI, fMRI, PET-CT, into 3D information in the patient's brain of a computational interface at the operating room [16]. The predefined targets on the navigational plan increase the chance to perform a safe and functional gross total resection of malignant primary brain tumors.

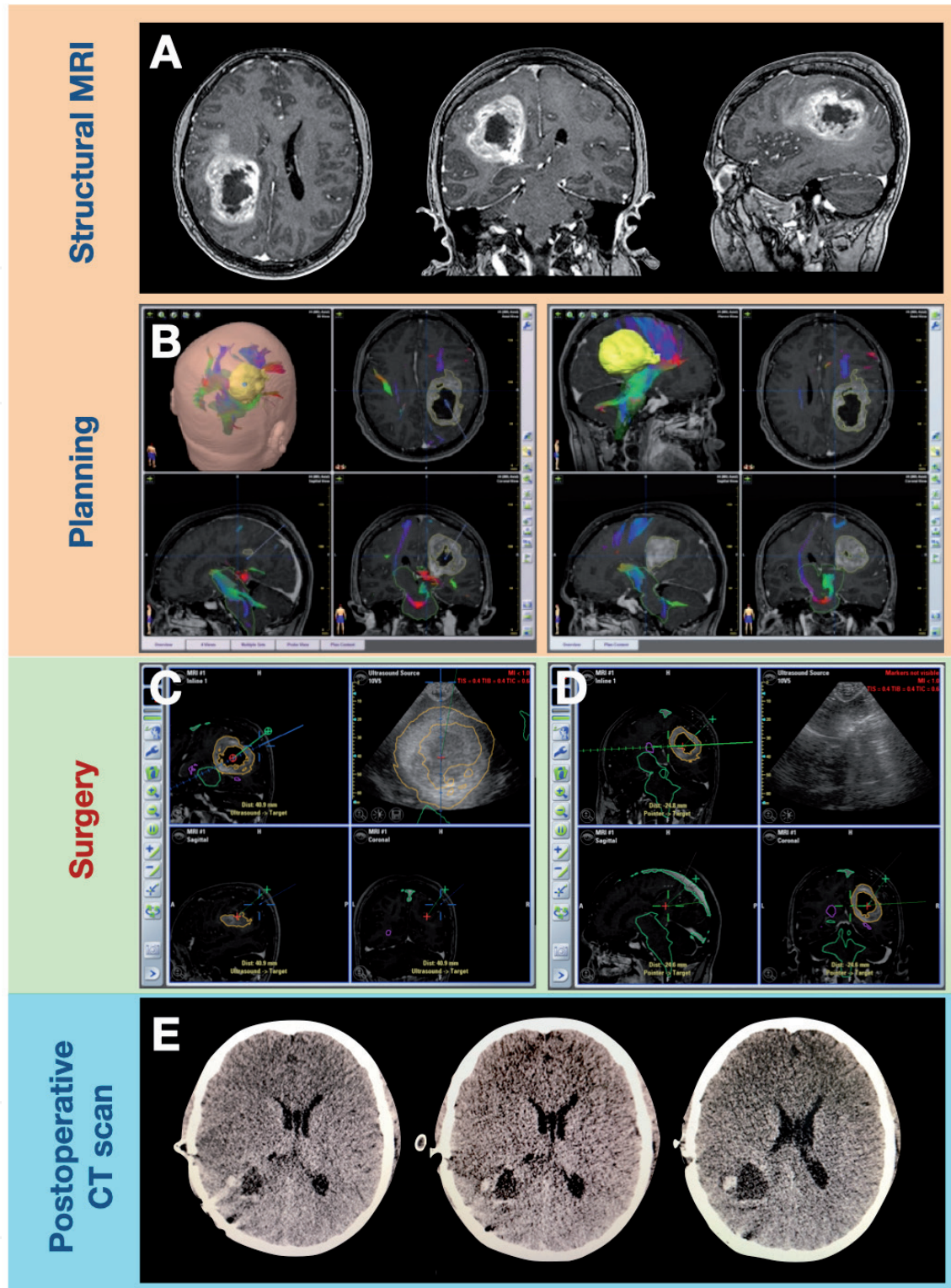
Its main objective is to facilitate the extensive resection of the lesion, minimize the risk of neurological sequelae, and favor the prognosis of survival. After registering the patient, the system's accuracy is checked by identifying constant anatomical references or craniometric points. The contour of the lesion and the functional data are fused on the reference structures. In some cases, it is possible to transfer the images to the surgical microscope's eyepieces during surgery.

The intraoperative accuracy of neuronavigation can be affected by changes in intracranial volume caused by tumor resection, brain inflammation, and cerebrospinal fluid flow **Figure 1**. Nevertheless, transoperative images can be combined with ultrasound, tomography, or magnetic resonance images. The intraoperative images offer the possibility of evaluating the residual tumor volume as the surgery progresses **Figure 6**.

##### 4.1 DTI and fMRI in functional neuronavigation

Neuronavigation is currently applied in brain surgery, and it is a regular technological resource to increase safety in most neurosurgical procedures (27).

The functional navigation was described as a technological tool for brain tumor resection. It results from the merging of structural, DTI, and BOLD information concerning a malignant tumor's localization. It allows us to know the precise location of functional areas in the human brain [28].



**Figure 6.** 3D intraoperative ultrasonographic reconstruction increases the usefulness of multimodal neuronavigation for brain tumor resection. A 17-years-old boy with a history of neurofibromatosis type 1 arrives at the emergency department with a headache and left hemiparesis. On an MRI study, a glioblastoma multiforme was suspected. (A) MRI T1-enhanced Gd images acquired for surgery planning at (B) Brainlab workstation. (C) 3D ultrasonographic acquisition to fusion with predefined neuronavigation's plan to achieve a gross total resection. (D) Immediate postoperative CT Scan.

Clinical articles have suggested that the brain shift observed after the opening of the dura and cerebrospinal fluid depletion is the main disadvantage for neuronavigation precision. Nevertheless, several reports suggest that intraoperative MRI use can solve this consequence of brain displacement satisfactorily [29]. In our country, these facilities are not available. To solve it, we correct the brain shift with

three-dimensional ultrasound (3D-US) scans before the dural opening, after the dural opening, and at the end of the resective surgery. Taking advantage of merging this new 3D-US information with previously developed navigation plans with information on the different modalities of structural, functional, and metabolic information tumor and the neighboring tissue. In order to preserve and restore the functional status of each patient. Some limitations to consider for applying these techniques are the biological variability among individuals, the displacement of deep brain structures, and the previously mentioned brain-shift.

## 5. Neuronavigation and intraoperative electrical stimulation

Prof. Hugues Duffau considers the brain as an entirely eloquent organ; every millimeter of the cerebral cortex represents, sometimes a well-recognized function, and others the association area for several complex functions as language and his diverse characteristics that sometimes define a person, visuospatial perception, auditive integration, and so forth.

In the pediatric patient, the patient's age determines a more complex scenario because the stage of neurodevelopment at the time of brain tumor surgery determines the functions' profile to evaluate. Some functions depend on the correct integration of cortical and subcortical areas in the developing brain. Thus, the extensive evaluation and integration in neuronavigation devices of structural, functional, and metabolic imaging techniques are essential to reduce the chance to produce functional sequels.

Undoubtedly, DTI has contributed substantially to the intraoperative identification of white matter tracts. Perhaps the most studied are those related to motor function. It has been widely described that subcortical continuous monopolar stimulation can help identify the pyramidal pathway with a comprehensive concordance with its counterpart visualized by DTI.

Transoperative electrical stimulation is one more of the resources available to promote extensive glioma resection. The purpose is to preserve the patient's functionality while attempting to dry out as much of the injury as possible [30].

In our experience, the integration of neuronavigation with intraoperative electrical stimulation and brain mapping considerably reduces the risk of lesions secondary to brain tumor resection.

Monopolar continuous stimulation seems to be the most useful and reproducible procedure for the pyramidal tract's subcortical characterization. With the aid of DTI, it is possible to identify the modifications preoperatively in the trajectory, density, and resultant distortion secondary to a CNS malignancy. The neuronavigation plan defines precisely the location of the pyramidal tract. In the operative field, the neuronavigation tools and the intraoperative monopolar stimulation can effectively identify its location at subcortical, thalamic, and peduncular regions.

Recently advances suggest that intraoperative acquisition of DTI images can reduce the risk of sequelae.

## 6. Conclusions

The current neuronavigational technologies allow us to reach deep regions inside the human brain without an increased risk of disability.

The interrelation of different radiological information modalities – structural, functional, and metabolic, in the planning phase of the case and during the surgical procedure permit us to increase the gross-total resection rate for brain tumor resection.

The integration of neurophysiological information into the neuronavigational platform during the neurosurgical procedure reduces complications by monitoring and stimulating with the matter tracts related to language and motor functions.

All multidisciplinary effort is directed to increase surgical techniques' safety to benefit the quality of life of children who suffer from brain tumor disease.

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Many people have changed my life, mom, sister, wife, son, and teachers. We acknowledge the incredible patient's confidence; thank you for touching my life, by improving yours.

This work is dedicated to respect and honor relatives and all medical staff members who fell during the COVID-19 pandemic.

## Conflict of interest

“The authors declare no conflict of interest.”

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