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RESEARCH ARTICLE

MULTIMODAL NEURONAVEGATION FOR BRAIN TUMOR RESECTION IN PEDIATRIC PATIENTS

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ABSTRACT

Primary central nervous system tumors originate from the neuroepithelial tissue, being the most common the gliomas. Nonspecific symptoms can include a headache, seizures, pyramidal syndrome and disorders of mental functions. Imaging studies provide critical information for the characterization of the location extension and other radiological features. The study of these neoplasms with nuclear medicine allows assessing more accurately the biological component of the lesion. Through the use of multimodal neuronavigation systems, it is possible to perform the integration of these different types of diagnostic imaging, increasing the precision and safety of surgical procedures. We present the case of a patient with a diffuse glioma of the right frontal lobe with a pyramidal syndrome which was operated by awake-craniotomy and multimodal neuronavigation-assistance. Currently, at 36 months of follow-up, the patient has full clinical recovery and no evidence of disease on PET scan.

INTRODUCTION

Clinical Case

A 17-year-old female who is evaluated for a condition of at least two weeks of evolution characterized by a decrease in the strength of the left half of the body and ipsilateral hypoesthesia. On physical examination, a left pyramidal syndrome was integrated. Imaging studies were performed and the diagnostic possibility of a diffuse glioma was considered due to the findings. Nuclear medicine studies with FET were requested and the diagnostic possibility of a diffuse glioma was considered. The patient was scheduled to undergo surgery to resect the lesion byawake-craniotomy. Transoperative neuropsychological evaluation and 3D ultrasonographic reconstruction were performed to guide the resection with a BrainLab® neuronavigation system.

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In the postoperative period, the patient recovered her previous neurological status without identifying sequelae at 36 months of follow-up or recurrence of the neoplastic lesion. Figure 1.

Background

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) (Kyle, 2017).

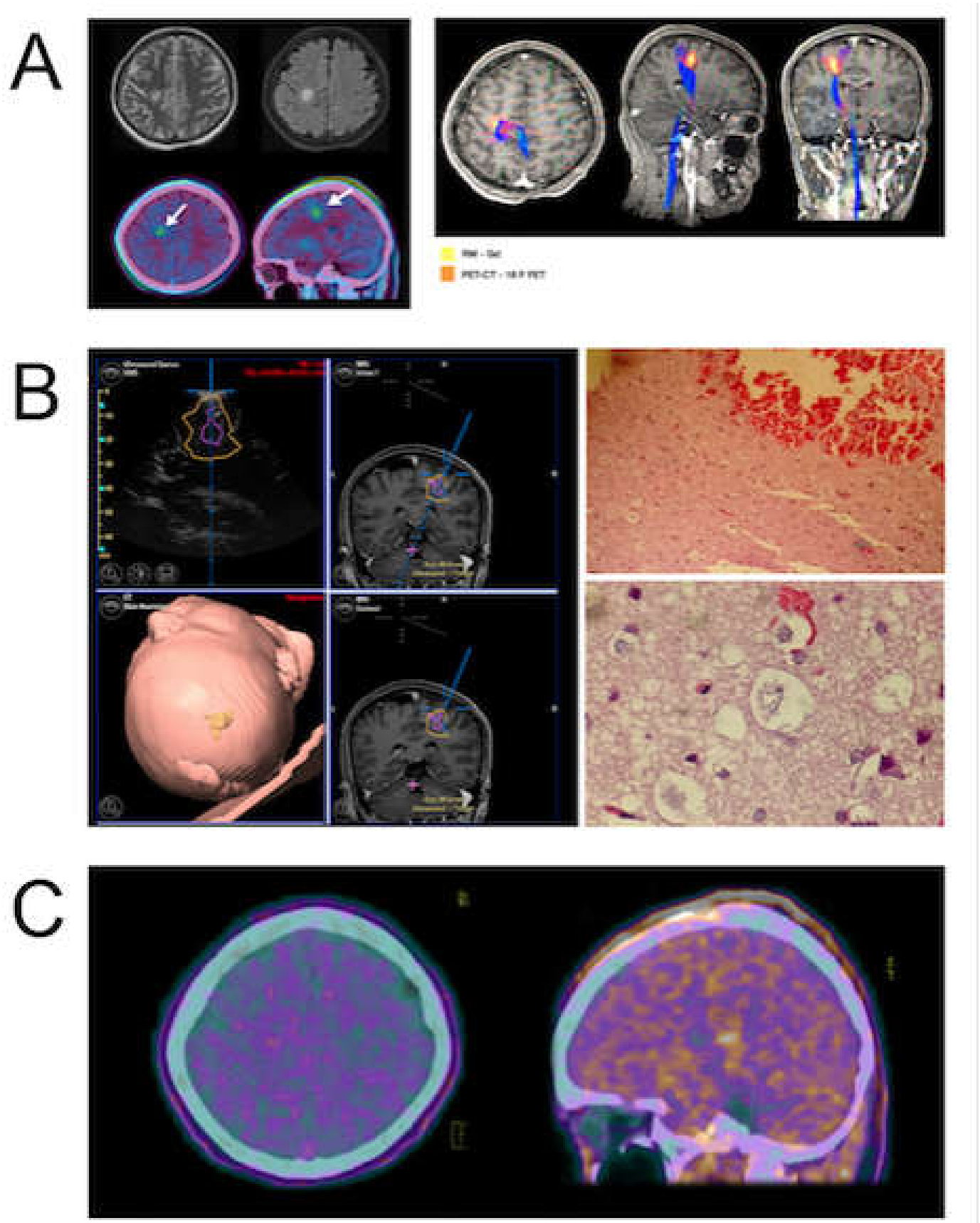

Figure 1. A) Right. RM T2 and FLAIR. An oval image is observed, well defined margins, hyperintense, located in the caudal portion of the second right frontal gyrus. PET-CT (18 F-FET) with uptake of the radiopharmaceutical at the site of the lesion. Left. Planning for multimodal Nueronavegación. Contrast MRI fusion, DTI, PET of the lesion. Various modalities of structural, functional and biological information are identified. B) Right. Images of transoperative neuronavigation with 3D ultrasonographic reconstruction. Left Images with astrocytic proliferation on a fibrillar background with moderate atypia. Up 10x. Down 40x. C) PET CT 18 F-FET postoperative. No uptake of the radiopharmaceutical was identified in the surgical site at 36 months of follow-up.

According to the classification of brain tumors of the World Health Organization (WHO), they are divided into gliomas of 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 consider anaplastic astrocytoma (grade III) and glioblastomamultiforme (grade IV), are characterized by a rapid growth rate, extensive infiltration of white matter and poor short-term prognosis (Floeth, 2005; Dunet, 2012). Therefore, the histopathological diagnosis and its proper classification is crucial for the treatment of patients. Diffuse astrocytoma (WHO grade II) is characterized by slow growth and infiltration of neighboring brain structures.

Histologically, it is constituted by well-differentiated fibrillar astrocytes or gemistocytic type. In general, this type of tumor affects young adults and tends to secondary progression towards malignant gliomas (anaplastic astrocytoma and glioblastoma multiforme). Diffuse gliomas represent 30-50% of astrocytic brain tumors in children. They are located in any region of the CNS, but more commonly they are located in the cerebral hemispheres. Survival time after resection surgery varies between 8 and 10 years, depending on the degree of initial resection. When more than 90% is resected, a real impact on the survival of patients is observed (Concha Enrique, 2017 and Consejo de Salubridad General, 2010). Survival of patients with low-grade tumors has been improved with the implementation of new diagnostic techniques and surgical treatment. The use of magnetic resonance imaging studies allows establishing with greater certainty the functional risks in the patient. Nuclear medicine studies allow the metabolic evaluation and predict the biological behavior of the neoplasms by indirectly evidencing intracellular metabolic processes - glucose, the rate of proliferation and cellular replication, through the recapture of amino acids and nucleosides, respectively (Filss, 2014). In pediatric patients, tumors of the central nervous system represent the second cause of cancer mortality, after leukemia (Tyler, 2016). The magnetic resonance represents the integration of different structural images (FLAIR, diffusion, perfusion, SPGR, TRUFFI), functional (DTI, BOLD) and metabolic (spectroscopy). For the evaluation of peritumoral edema diffusion and perfusion sequences are used (Lily, 2014; Michael Lundemann, 2017). The use of sequences that provide functional information allows the early identification of the risks associated with neurosurgical treatment and the functional prognosis of each case (Tyler, 2006).

The use of nuclear medicine for metabolic characterization and cell proliferation is recent in our country. There are reports that 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. Part of the basic principles of stereotactic surgery, by identifying a point in space following coordinates in a conventional Cartesian plane. The acquisition of images that evaluate different aspects of the neoplasm facilitates the surgical approach of these lesions, by allowing guided image surgeries with a lower risk of morbidity and mortality. The combination of different imaging modalities allows to integrate the structural profile of the lesion with the metabolic information, thus achieving a better delimitation of the biologically active component of the tumor, avoiding contamination of the target to be treated by cerebral edema. [12]

Characteristics of Image Studies to Perform Neuronavigation

Diffusion tensor (DTI)

The diffusion tensor images allow the visualization and characterization of the tracts of fibers of white matter (Lily, 2016; Guo, 2011). Its usefulness has been described since 1994, it has 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 diffusion of water is directed by the anatomical microstructure; being an eco-planar technique that maps the speed of diffusion of water (Jenkinson, 2007). In brain tissue, diffusion rates are slower due to the normal parenchyma components that impede water movement. In certain pathological processes, the diffusion of water is restricted, which reduces apparent diffusion coefficient (ADC), as in acute infarcts secondary to cytotoxic edema, abscess, lymphoma (Lily, 2014 and Yamasaki, 2005). Fiber tracking is the only non-invasive method to visualize the course, displacement or interruption of the main tracts of white matter according to the DTI technique. Multiple studies have shown that fiber tracking can reconstruct the major fiber structures of white matter in the brain. The identification of 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 completely eliminated or when the 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 x 128, field of view, 251 x 251 mm, thickness of cut, 3 mm, bandwidth, 1502 Hz per pixel, diffusion encoding gradients in 12 directions with b values of 0 and 1000 s / mm2, and voxel size, 1.9 x 1.9 x 3 mm) (Guo –Chen Sun, 2011; Lily, 2014 and Borogovac Ajna, 2012). The 3D segmental reconstruction of the tumor is performed on the basis of 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 cavernoma, represented the limit of segmentation. In the case of non-enhancing lesions such as low-grade glioma, the T2-weighted image is used to determine the edge of the tumor. For this reason, most tumors that do not have post-contrast enhancement have optimal visibility in this sequence. The existence of an important edema, which can not be clearly distinguished from the low-grade glioma, was ruled out based on the findings of inversion 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 (Guo – Chen Sun, 2011).

Perfusion by Magnetic Resonance

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 the passage of blood that has been marked with contrast material. Theoretically, the degree of signal drop is proportional to the concentration of gadolinium in the tissue, obtaining relative curves of concentration - time. Obtaining cerebral blood volume rCBV (cerebral blood volume), CBF (cerebral blood flow), MTT (average transit time). Dynamic contrast images weighted in T1, where the main focus is the estimation of tumor permeability, allowing the contrast to filter into the extravascular space and reach equilibrium during several passes of contrast bolus through the tumor bed. 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 (Borogovac Ajna, 2012; Covarrubias, 2004; Guzmán-de-Villoria, 2012; Cha, 2003). 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) (Thompson, 2010). However, in the case of low-grade astrocytomas, they tend to have a high cerebral blood volume, associated with the process of angiogenesis and dense capillary networks that characterize these tumors (Cha, 2005).

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 multivoxel technique, in which a greater volume of tissue is evaluated (Bendszus, 2000). The main metabolites evaluated include N-acetyl aspartate (NAA) (normal 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, the majority of CNS tumors manifest with elevated choline-creatine and co-NAA ratios caused by increases in cellularity (choline elevation) and relative decrease in normal neurons (reduction of NAA) (Oscar, 2009).

Utility of nuclear medicine in cerebral tumors

In Mexico, the use of PET positron emission tomography equipment began with the opening of the PET-Cyclotron Unit of the National Autonomous University of Mexico in 2002.
Nuclear medicine in brain tumors has been used to indirectly suggest the degree of malignancy of the lesions, for the staging, to evaluate the response to treatment, the detection of recurrence and the planning of radiotherapy. By obtaining functional information of cellular and biological processes, including glucose metabolism, protein synthesis. The PET with 18 fluoro-deoxy-glucose (FDG) PET was initially used to detect and distinguish tumors of 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 very useful for taking biopsies guided by (Vincent, 2016 and Floeth, 2005), image to establish the diagnosis of primary brain tumor (Vincent Dunet, 2016 and Dunet, 2012), in the planning of radiotherapy treatments and to distinguish between tumor recurrence or radionecrosis after initial therapy (Vincent Dunet, 2016; Bolcaen, 2015). 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 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 (Filss, 2014 and Gempt Jens, ?). Since 18-FDG is unreliable for predicting the neoplastic nature of a lesion 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 populations of small patients directly in directly compared the diagnostic value of 18-FDG and 18-FET. Goldman and Pirotte thoroughly reviewed the clinical management, images and role of PET (Goldman, 2011). The results obtained with the uptake of 18-FDG PET and the enhancement with the MRI have been reviewed and reported by a consortium of pediatric brain tumors with various findings in a spectrum of tumors where they varied according to the type of tumor. 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 trochanter gliomas, the poor correlation between uptake and enhancement is associated with a decrease in patient survival, as it may reflect concurrent tissue degradation in the disease sites that received treatment and the development of new sites of malignancy characterized by increased uptake of 18-F-FDG (Zukotyrski, 2014)

Neuronavegation

Neuronavigation systems represent a digital alternative for the three-dimensional processing and recognition of anatomical structures in the operating room. Images of sequences enhanced in T1 post-contrast 3D are used. Functional data of DTI or functional MRI are used to identify the relationship of eloquent areas of the brain with tumors (Karl Herholz, 2017; Yamasaki, 2005). Also, ultrasound images in three-dimensional version, as a source of intraoperative real-time image, updates each new control, delivering accurate anatomical information, unaffected by some displacement of brain tissue that may occur during surgery, each ultrasound evaluation It only takes a few minutes to run and therefore does not delay the usual surgical times (Francisco Mena, 2017). The main objective of its use in resection surgery of brain tumors is to facilitate the extensive resection of the lesion, minimize the

risk of neurological sequelae and favor the prognosis of life. After registering the patient, the accuracy of the system is checked by identifying constant anatomical references or craniometric points. The contour of the lesion and the functional data are superimposed on the neuromarker, in some cases it is possible to transfer the images to the eyepieces of the surgical microscope 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. To solve this problem, transoperative images can be obtained with ultrasound, tomography or magnetic resonance. The intraoperative images offer the possibility of evaluating the volume of tumor as the surgery progresses (Guo –Chen Sun, 2011).

DISCUSSION

Multimodal neuronavigation allows integrating the information obtained from different imaging modalities - tomography, magnetic resonance and PET. In this way, it is possible to establish with high precision, the structural, functional and metabolic information of an anatomical region, which in the case of brain tumor surgery will determine the risk of morbidity associated with resection. It has been described that 18 F-FET has a high sensitivity and specificity for the diagnosis of brain tumors (82 and 76%, respectively). In our case, a good concordance was identified between the structural (MR-Gd), functional (DTI) and metabolic (PET) images of the lesion. Thus allowing an extensive resection, without loss of functionality of the patient. However, it should be noted that there are other radiopharmaceuticals to identify intracranial PET / MRI tumors: FDOPA useful for monitoring patients with glioma in antiangiogenic agents. MET has been shown to be able to localize improvement in gliomas. FMISO predicts provides an imaging marker of tumor hypoxia, a prognostic factor established for poor response to radiation therapy (Tyler, 2016). The combination of such modalities with the use of biological PET information, especially with radiolabel amino acid analogs, could lead to more detailed treatment planning and generation of failure analysis models in the future, as also mentioned in the recommendation recently. published the combined effort of the European Association of Neuro-Oncology (EANO) and Evaluation of response in groups of Neuro-Oncology (RANO) (Albert, 2016).

Conclusion

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 various techniques. Its use in multimodal neuronavigation platforms allows to increase the usefulness of radiological information when transferring the findings to the three-dimensional structure of the patient during the performance of surgical procedures. It should be noted that patients with glioma, tumor heterogeneity challenges tumor resection, due to lack of precision over actual extension, proliferation capacity, which is why numerous studies using PET / MRI fusion, with positron emission as 18 F - Fluoro-ethyl-tyrosine can greatly increase diagnostic accuracy and tissue differentiation in uncertain cases; This facilitates the neurosurgeon, for the anatomical structural identification, planning of the surgical strategy, reduction, centering of the craniotomy and thus not prolonging the surgical time and decreasing the hospital stay. The PET / MRI fusion in the same way in the postoperative and radio oncological treatment provides information for tumor response, progression and necrosis by radiation, providing the oncological and functional prognosis of the patients.

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