DEPARTMENTAL FACULTY OF MEDICINE AND SURGERY

Bachelor's Degree Course in Radiology, Diagnostic Imaging and Radiotherapy techniques

^{18}F-FDOPA PET/CT SUV derived-indices and volumetric parameters correlation in patients with primary brain tumors

Dissertation of

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Title

The relationship between ^{18}F-FDOPA PET/CT SUV derived indicators and volumetric measures in patients with primary brain tumors.

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Abstract

Neuroimaging is important in the diagnosis of intracranial cancers, particularly brain gliomas, and must include an assessment of the tumor's location, size, and biological activity. As a result, morphological imaging modalities should be paired with functional, metabolic, or molecular imaging modalities for primary diagnosis, as well as for tracking the course and evaluating therapy benefits.

Next, amino acid radiotracers such as ^{18}F-FDOPA are being evaluated in the management of brain diseases, especially neoplastic diseases. ^{18}F-FDOPA PET is a promising additional tool in the management of glioma, the most common primary brain tumor in children and adults, consisting of a group of heterologous neoplastic diseases originating from sustentacular cells of the central nervous system (CNS) (glial cells). Their histopathological and molecular characteristics are quite different, as are their management and prognosis. However, radiolabeled amino acids for positron emission tomography(PET) can be used to more precisely delineate tumor margins, improve targeting of biopsy and radiation therapy, and improve surgical planning. Additionally, amino acid imaging is used to distinguish tumor recurrence from nonspecific post-treatment scar tissue, to predict the prognosis of low-grade gliomas,and to monitor metabolic responses during treatment.

New parameters for PET imaging, such as volume parameters, are gaining increasing interest in the scientific literature, but with the role of dopaminergic tumor volume (DTV) and total lesion F-DOPA activity (TLDA) and SUV volume parameters. Derived parameter correlations are not yet well defined. This retrospective study included 133 patients who underwent ^{18}F-FDOPA imaging for primary brain tumors. Indicators derived from SUVs were calculated (the occipital lobe was selected to generate the SUV ratio of the tumor) and compared to the volume parameters. The regression model is applied to univariate analysis, where SUV max is positively correlated with DTV (beta 0.42, $p=0.007$) and SUV max ratio is positively correlated with DTV (beta 0.80, $p=0.011$). Then there was a positive correlation. At TLDA (beta 1.27, $p<0.0001$), the maximum SUV ratio was positive at TLDA (beta 1.87, $p<0.0001$). Our study shows that PET/CT ^{18}F-FDOPA volume absorption parameters are easy to assess in primary brain tumors with

high SUVmax to SUVmax ratios and support a new role for volume parameters in interpretation.

Introduction

1.

Positron emission tomography (PET) with the amino-acid analog 3,4-dihydroxy-6-^{18}F-fluoro-l-phenylalanine (^{18}F-FDOPA) is one in all the foremost used imaging techniques within the management of primary head tumors, more than ever for cancer grading, explanation of lump extension, healing planning, behavior answer and post-treatment surveillance. This radiopharmaceutical could be a catecholaminergic precursor, and it enters the cellular compartment through L-type amino acid compound transporter 1 and 2 (LAT1 and LAT2), overexpressed in cancer cells. Inside the cell chamber ^{18}F-FDOPA is decarboxylated by aromatic l-amino acid decarboxylase with the formation of ^{18}F-dopamine then is transported into vesicles: the bigger protein synthesis induces a prominent uptake of the radiopharmaceutical in cancer cells.

The current classification of central nervous system tumors by the World Health Organization (WHO) (2016) describes primary brain tumors that support histopathological features and molecular genetic alterations. The possible effects of those characteristics on ^{18}F-FDOPA uptake in primary brain tumors are studied: as an example, the correlation between ^{18}F-FDOPA uptake in tumor cells and glioma grade was analyzed by several authors and had high radiotracer uptake in high-grade gliomas. In addition, the possible effects of molecular genetic alterations in glioma on amino acid metabolism were calculated with^{18}F-FDOPA PET/computed tomography (CT) has been investigated, showing no significant correlations in two studies.

The use of the standardized absorption or uptake value (SUV) is common in clinical practice to assess the absorption of radiopharmaceutical by cancer damages in PET/CT analyzes: the SUV is calculated as tissue radioactivity ratio concentration to a given time, divided by a dose during injection divided by a weight of the body. In addition, the absorption of cancer is generally evaluated with SUV indices as SUV max, SUV mean, SUV max ratio or report, SUV mean ratio. Indices derived from PET ^{18}F-FDOPA SUV are systematically available information that also allows precise low-level discrimination and high-grade gliomas. However, the precise methodology for a

complicated SUV report is not determined; mainly, it's not all-including the selected background region to generate cancer absorption relationships.

This study aims to focus on how to calculate the maximum SUV ratio, based on a previous study from our research group, in which the occipital region was selected to generate the tumor SUV ratio. However, new parameters for PET imaging, such as volumetric parameters, are of interest in the scientific literature. Several studies, and meta-analyzes on ^{18}FDG-PET/CT have focused on the increasing role of volume parameters in several cancers categories. Most of the published articles on the prognostic value of the volumetric parameters are related to nasopharyngeal cancer, and some focus on the thorax (Non-Small Cell Lung Cancer, breast cancer, esophageal cancer) and other carcinomas. Volumetric measurement role in ^{18}F-FDG imaging, especially at the prognostic stage. However, the role of the ^{18}F-FDG PET volume parameter in brain tumors is still controversial. Several articles have been published focusing on the area of the neck and head. Volumetric parameters(metabolic tumor volume) [MTV] and total lesion glycolysis [TLG] are factor-independent prognosis, according to previous systematic studies of the parameters used in PET 18F-FDG imaging of the neck and head region. The prognosis value is the maximum standard absorption value (SUV max). Volumetric parameters (MTV and TLG) appear to be associated with the identification of patients at high risk of postoperative disease progression who may benefit from early therapeutic intervention to improve prognosis. Other papers confirm that MTV and TLG have higher prognostic values than SUVmax and that MTV and TLG can be used as prognostic biomarkers to predict outcomes in patients with head and neck cancer. However, the assessment of volume parameters in ^{18}F-FDOPA imaging is not routine, and as far as we know, several studies have been published. The method of calculating the volume parameters is similar for ^{18}F-FDG and ^{18}F-FDOPA imaging, but the output is different. Dopaminergic tumor volume instead of metabolic tumor volume, whole lesion F-DOPA activity instead of whole lesion glycolysis. However, like the volume parameters for ^{18}F-FDG PET/CT imaging, the volume parameters for ^{18}F-FDOPA imaging appear to be potential support during the prognostic stage. In addition, as far as we know, in the assessment of primary brain

tumors using ^{18}F-FDOPA PET/CT, SUV-derived indicators, dopaminergic tumor volume (DTV), total lesion F-DOPA activity (TLDA), etc. There is a correlation with the volume absorption parameter. Not yet clearly defined. This study includes SUV-derived indicators and volume absorption parameters in PET/CT ^{18}F-DOPA scans of patients with primary brain tumors to improve their knowledge of parameters that may affect the management and image analysis of primary brain tumors with the purpose is to evaluate the correlation. This type of functional imaging, which is Positron emission tomography(PET), can non-invasively measure biochemical information about the tumor and surrounding tissues. PET imaging is also in a unique position to identify ideal cases of targeted treatment and assess the progress of treatment. This article provides an overview of the new imaging tracer used in PET imaging of brain tumors.

The discussion includes the strengths, limitations, and pitfalls of individual biomarker imaging strategies, as well as general challenges related to PET imaging of brain tumors. First, we will outline the established PET imaging biomarkers(glycolysis, amino acid metabolism, DNA replication, hypoxia, and inflammation).

2.Overview of PET contrast media for Brain Tumors

2.1. Sustained growth Markers: Glycolysis, Amino Acid Transport, and DNA Replication.

The classic approach to imaging tumors in general, and its application to Glioblastoma polymorphism or multiforme(GBM), was to examine the functional need for growth. These essentials include glucose metabolism, protein synthesis, and DNA replication. From a biochemical point of view, these functions emphasize the small molecules «building blocks» (sugars, nucleotides, bases, amino acids) that make up macromolecules.

The radionuclide-labeled morphology of these building blocks has been used to study these functions in PET imaging. The gold standard for most cancer imaging is ^{18}F-FDG, an analog of fluorine-18 glucose. This radioactive tracer is actively absorbed by the glucose transporter, participates in the first stage of glucose metabolism (phosphorylation), and is encapsulated inside the cell. ^{18}FDG PET enables functional imaging of glucose metabolism, a relative gold mine of information in most cancers.

However, the natural high uptake of ^{18}F-FDG in the brain complicates the interpretation of glioblastoma lesions near the gray matter. Other efforts to image growth through the «building block» strategy include neutral amino acid analogs(^{11}C methionine; ^{18}F fluoroethyl-L-tyrosine; ^{18}F-Fluorodopa and deoxynucleoside bases(^{18}F-Fluorothymidine and ^{18}F-Clofarabine).

The nonessential amino acid and dopamine neurotransmitter is also used as a PET tracer in the form of ^{18}F L-fluoro-dihydroxyphenylalanine(^{18}F-FDOPA), which becomes a dopamine analogue in vivo after decarboxylation. The ^{18}F-Fluorodopamine is then incorporated into the vesicles by VMAT or metabolized by monoamine oxidase or catechol-*O*-methyltransferase. This makes ^{18}F-FDOPA of particular utility in neuroendocrine tumors, in addition to its obvious neurological uses. ^{18}F-FDOPA imaging in patients with preoperative glioma falls between WHO grade and MRI contrast enhancement degree, T2 hyperintensity degree, and ^{18}F-FDOPA uptake(as a ratio SUVmax from tumor to normal tissue) shows a significant correlation with. From this cohort of 45 patients, multivariate Cox regression suggested that ^{18}F-FDOPA PET and age were important prognostic factors for overall survival. The main limitation in the use of ^{18}F-FDOPA is radioactive synthesis. One of the first high-efficiency radiosynthesis described was associated with electrophilic fluorination. Electrophilic fluorination is not the preferred method for routine clinical production due to the dangerous nature of F2 gas, but improved synthesis involving nucleophilic fluorination has recently been announced.

3.General imaging consideration

PET imaging of the brain for all medical conditions is a challenge. The blood-brain barrier (BBB) is a major obstacle to effective radiotracers targeting glioblastoma. Even if the radiotracer invades the brain, many compounds show slow invasion into the brain (i.e., low K1 values). Since glioblastoma lesions often impair BBB, increased radioactivity levels at the site of injury may reflect an increase in non-specific radiotracers in lieu of, or in addition to, an increase in target signal. For example, a study combining [^{18}F]FMISO PET and MRI showed high uptake of [^{18}F]FMISO not only in necrotic tissue but also in areas of BBB injury. This poses a challenge in quantifying

suspicious glioblastoma lesions. Kinetic modeling approaches that incorporate dynamic data can sometimes help distinguish non-specific signals from specific signals. Although these scan protocols may require longer scan times and perhaps arterial blood sampling, the potential for improved quantification of specific radiotracer uptake is when PET is used to image GBM. It provides important benefits in assessing diagnostic, staging or therapeutic efficacy to be considered.

The reference region approach can reduce scan time and provide an alternative to quantitative analysis that does not require arterial blood sampling. Such an approach has significant limitations for ubiquitously expressed targets such as TSPO, but for brain tumor imaging, the reference region can be depicted as a larger region that is removed from the lesion. For example, in the case of FET imaging [^{18}F], a fixed-sized reference ROI was placed in the contralateral hemisphere of the tumor tissue, resulting in complete image-derived measurements that correlated with non illness survival. The input functions derived from the image allow other non-invasive modeling approaches. For example, [^{18}F]FMISO does not have a reference area, but the tissue/blood ratio obtained from the image provides a reasonable approximation of the parental radioactivity measured in venous blood. Such an approach makes it possible to maintain quantitative precision while reducing the logistical complexity induced by a complete dynamic analysis with blood sampling.

The last major obstacle to PET radiotracer imaging of GBM is high nonspecific binding. If the non-neoplastic brain region has very few specific binding, a radiotracer with weak non-specific binding may be suitable for analysis of the reference region. Another related challenge is off-target binding. For example, the sigma 1 and sigma 2 receptors have structurally significant similarities to opioid receptors. These challenges underscore the need to block testing with candidate radiotracers to ensure proper sensitivity and specificity without high non-specific binding.

Chapter 1

This first chapter discusses the types of primary brain tumors, how to diagnose the primary brain tumors, the contribution of positron emission tracers(^{18}F-FDOPA PET/CT) in the management of gliomas (Focusing on Glioblastomas), and evaluation. The purpose is to explain how differences in radiopharmaceuticals used compared to ^{18}F-FDOPA , parameters associated with ^{18}F-FDOPA , and molecular imaging in pediatric brain tumors.

1.Types of primary brain tumors

1.1. What is a glioma?

Glioma are a type of tumor that begins in the glial cells. Glial cells surround and support neurons in the brain and other parts of the nervous system. Glioma is one of the most common types of primary brain tumors. They can be low level or grade(slow growing) or high level(fast growing). Low-grade gliomas can develop into high-grade gliomas over time. There are several types of gliomas. Their names indicate the type of cell in which they start:

- Astrocytomas affect glial cells called astrocytes. The most invasive astrocytoma is glioblastoma, also called polymorphic glioblastoma.
- Oligodendroglioma affects glial cells called oligodendrocytes.
- Mixed gliomas include both astrocytes and oligodendrocytes.
- Ependymoma affects the cells that line the hollow chambers of the brain(ventricules) and the central canal of the spinal cord.

1.2. Glioblastoma

Glioblastoma is the most malignant brain tumor in adults. Tumors begin with astrocytes, which support nerve cells in the brain in a variety of ways. Glioblastoma can metastasize (metastasis) through brain tissue and can be difficult to remove.

1.3. Primary Lymphoma of the Central Nervous System The cancer begins in the lymphocytes of the lymphatic system. Lymphocytes are designed to help fight illness and infections. Lymphocytes in the brain, eyes, spinal cord, or the three membranes that line the brain and spinal cord(called the meninges) can become cancerous and begin to

grow and spread out of control. PCNSL is common in people with weakened immunity. Lymphoma of the central nervous system of the eye is called ocular lymphoma.

1.4. Tumors in the pineal gland area

Pineal tumors begin in the small endocrine pineal gland and surrounding cells deep in the brain and secrete hormones directly into the bloodstream. These tumors can cause problems if they block the flow of cerebrospinal fluid, compress brain tissue, or block hormone production. They can be of lower or higher quality, grade. There are two main types of pineal tumors: germ cell tumors that begin with germ cells(eggs or sperms) around the pineal gland and pineal tumors that begin with pineal cells. Gliomas can also arise from glial cells in the pineal gland.

1.5. Pituitary tumor

They start with the epithelial cells that line your pituitary gland, which helps control the release of hormones from other glands in your endocrine system. These tumors can cause overproduction of pituitary hormones, which in turn can lead to a variety of other disorders.

1.6. Meningioma

Meningiomas start with the membrane that surrounds the brain inside the skull. Most meningiomas are slow growing non-cancerous tumors, but they can also become cancerous. These tumors cause seizures in about 25 % of people.

1.7. Acoustic Nerve Sheath Tumor

Acoustic neuroma(vestibular schwannoma) is a type of non-cancerous tumor that starts in Schwann cells and wraps around peripheral nerves in the ear. These tumors can cause hearing and balance problems. Most grow very slowly. As an acoustic neuroma grows, it compresses nearby nerves and blood vessels, as well as the surface of the brain stem and cerebellum. This pressure can cause neurological problems.

2.How to diagnose a primary brain tumor?

Management of primary brain tumors is based on magnetic resonance imaging(MRI). Despite the progress of MRI as a perfusion and diffusion technique, it has many limitations(mainly due to the destruction of the blood-brain barrier), in particular to distinguish recurrence from post-treatment effects. Additional magnetic resonance

spectroscopy has been developed to improve sensitivity and specificity. However, this approach is controversial due to the overlap between low grade tumor values and high grade tumors values. Its use to distinguish recurrence and near-progression is under study.

Distinguishing between low-grade and high-grade features of primary brain tumors and identifying patients who have relapsed and those with pseudo-advanced are important in choosing the best treatment. Computed tomography/positron emission tomography(PET/CT) has the potential to be a tool to support each of these goals, given the large number of radioisotopes available in a variety of clinical situations.

18 Fluorine-fluorodeoxyglucose (^{18}F-FDG) PET/CT is widely used in oncology and can also provide relevant information for the treatment of primary brain tumors. Nonetheless, high rates of glucose metabolism in normal brain tissue(low signal-to-noise ratio to tumors), low glucose metabolism tumors(such as low-grade gliomas), and ^{18}F-FDG specificity. The lack remains the limit. For these reasons, these unrestricted alternative PET radiotracers have been evaluated relatively recently in the management of brain tumors.

Amino acid radiotracers are poorly absorbed in normal brain tissue. Hence, it is easier to clarify brain progress like neoplastic disease. Several radiolabeled amino acids are currently in use. The first of these was ^{11}C-methionine(MET). However, its use is limited because carbon 11 has a half-life of 20 minutes and is reserved for PET centers with cyclotron units on site. [^{18}F] other fluorine-18 labeled amino acid radiotracers, such as -L-dihydroxyphenylalanine(^{18}F-FDOPA), have been synthesized and have a long half-life (110 minutes), which makes them easy for use in clinical routines. According to studies, ^{18}F-FDOPA PET/CT is better than ^{18}F-FDG PET/CT, it has been shown to be accurate and sensitive to detection of primary or recurrent glioma. Several studies have shown that these different amino acid radiotracers(^{18}F-FET, ^{11}C-MET and ^{18}F-FDOPA) work equally well in the visual assessment of primary brain tumors. In addition, the mechanisms that separate the cell membranes of amino acid radiotracers are active, and their uptake appears to correlate with glioma grade. This is primarily due to increased amino acid transport to tumor cells via overexpression of the L amino acid transport system (LAT 1

and LAT 2). With Youland et al. there was a statistically significant positive correlation between median SUV of ^{18}F-FDOPA and LAT 1 expression (p=0.04).

Radiotracers of amino acids, such as ^{18}F-FDOPA, affect the treatment of patients with primary brain tumors. Its use is currently recommended by the joint guidelines of EANM, EANO, and RANO for some indications. However, it is still important for future research to standardize acquisition and interpretation parameters. This systematic literature search seeks to summarize data on the usefulness of ^{18}F-FDOPA PET for the diagnosis and management of primary brain tumors.

3. Contribution of ^{18}F-FDOPA in management of primary brain tumors

^{18}F-FDOPA originally distributed dopamine in patients with motor disease as a dopamine precursor that enters brain tumors via the L-amino acid transporter (LAT) without significant absorption into the surrounding brain parenchyma except the ganglia used to evaluate. Potential interest in ^{18}F-FDOPA in the search for brain tumors was first reported by the accidental discovery of grade II oligoastrocytoma with ^{18}F-FDOPA in patients with suspected dyskinesia and underlying Parkinson's disease.

Although ^{18}F-FDOPA uptake is significantly associated with LAT-1 expression, the linear correlation between LAT-1 expression levels and binding strength is still debated. ^{18}F-FDOPA transported by tumor cells does not remain trapped. BBB permeability can have additional complementary effects and can be added to increased expression of amino acid carriers in high-grade tumors.

^{18}F-FDOPA combines the successful biopharmaceutical properties of amino acids with the practical physical and logistical properties of fluorine-18. It could replace ^{11}C-methionine in imaging the amino acid transport of glioblastoma. Visual analysis and SUV ratio of ^{18}F-FDOPA to ^{11}C-methionine suggests that it is a good surrogate for finding recurrent lesions, especially in centers without cyclotrons on site. ^{18}F-FDOPA can help classify newly diagnosed gliomas, plan radiation therapy, and assess response to treatment. Another advantage is that the images can be taken 20 minutes after injection without interfering with the delay in physiological fixation of the basal ganglia, which peaks later.

^{18}F-FDOPA is used to distinguish between high grade and low grade. Absorption of ^{18}F-FDOPA prior to treatment for newly diagnosed gliomas has been reported to correlate with tumor grade and growth. No significant correlation has been reported for recurrent gliomas. Depending on the increase, the correlation between uptake and tumor aggression can distinguish between low grade and high grade tumors. Clearly, thresholds of SUVmax have been reported. It should be noted that tumor uptake from glioblastoma may be lower than uptake from oligodendrogliomas. Janvier and his colleagues may be able to better distinguish between low-grade and high-grade tumors in routine practice with other indicators such as SUVmean tumor/ brain normal ratio or SUVmean tumor/striatal ratio.The kinetics and uptake of ^{18}F-FDOPA revealed differences between high-grade and low-grade tumors, in particular the time–activity curve. High-grade tumor profiles show an initial maximum, followed by a sharp decline, while low-grade tumors show a slow decline curve. In contrast, a few rare studies failed to demonstrate a difference in the absorption of ^{18}F-FDOPA between low-grade gliomas and high-grade gliomas. This may be linked to the limitation of the statistical power and to the difference in inspection time and in the acquisition time of the images.

Biopsy site guide ^{18}F-FDOPA: the intensity of the intake is related to the grade. Therefore, ^{18}F-FDOPA can identify high definition areas and areas likely to benefit from radiotherapy stimulation.

However, ^{18}F-FDOPA in the radiation therapy program was disappointing. This allows for a wider depiction of the tumor and a significantly wider contour of total tumor volume (GTV) than defined by MRI alone. However, the therapeutic effect was weak because almost all recurrences occurred apart from PET-GTV.

^{18}F-FDOPA is very helpful in distinguishing between radiation necrosis and recurrence of glioblastoma. Visual analysis based on 5-point visual scale or semi-quantitative imaging using brain tissue from striatal or normal injury accurately recurs from treatment-related changes in 110 patients who followed glioblastoma it was

distinguishable and had a prognosis for PFS. Patients with a positive test had 4.2 times shorter median OS than patients with a negative test.

The superiority of ^{18}F-FDOPA over ^{18}F-FDG has been reported in the evaluation of recurrent tumors and in the distinction between tumor recurrence and radionecrosis due to the high contrast between tumor tissue and normal tissue. The sensitivity of ^{18}F-FDOPA was greater than that of ^{18}F-FDG on visual analysis, but was comparable, and poor specificity was reported. Addition of semi-quantitative analysis by determination of the ^{18}F-FDOPA ratio [tumor/striatal ratio (T/S), tumor/normal white matter ratio (T/W), and tumor/contralateral normal brain tissue ratio (T/N)] improved specificity. When the T/S ratio was 0.75, the maximum sensitivity was 100% and the specificity was 86%, but when the T/S ratio was 1.0, the sensitivity was slightly reduced to 92% and the specificity was 95%. A cutoff of 1.0 prevailed in the primary assessment or clinical suspicion of radionecrosis, and a cutoff of 0.75 was the most likely assumption in inconclusive or suspected cases of tumor recurrence (Figure 1). Another study confirmed these results more precisely.

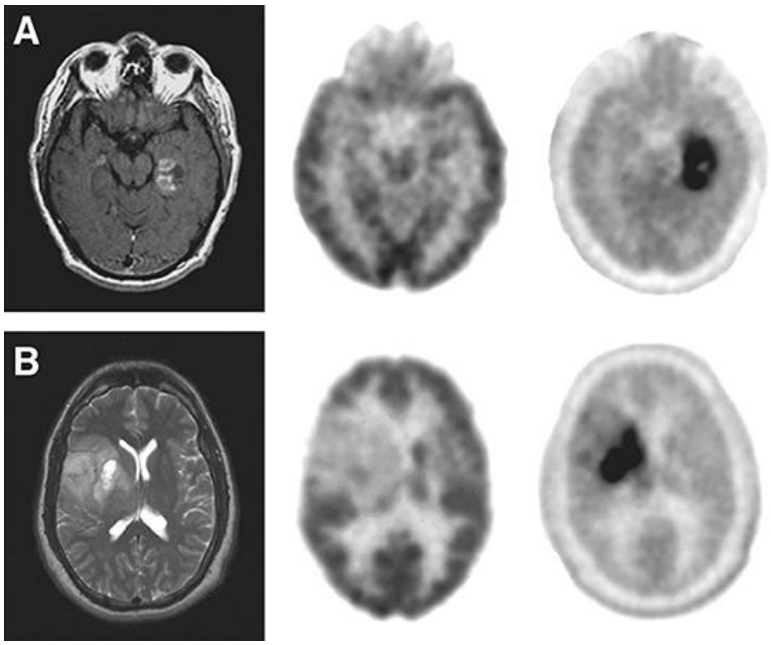

Figure 1. MRI of newly diagnosed tumors (left), ^{18}F-FDG PET (center), and ^{18}F-FDOPA PET (right). (A) Glioblastoma (B) Grade II oligodendrocyte glioma. This study was originally Chen et al. it was published in.

Postoperative macrophage activation reports rare false-negative glioblastoma and several false-positive lesions such as acute disseminated encephalomyelitis,

neurosarcoidosis, demyelinating lesions and inflammatory granulation tissue at the margin of excision has been done. Therefore, uniform circumferential fixation with weak excision edges is not associated with tumor recurrence, but can be caused by postoperative inflammatory changes and can be closely monitored.

Ratio of ^{18}F-FDOPA as a prognostic factor: tumor (T/N) to normal tissue was significantly associated with survival in patients with suspected recurrence of glioma. In low-grade gliomas, fixation strength may be an independent predictor of disease progression, suggesting its prognostic role. However, unexpected and somewhat paradoxical results showed a higher uptake of ^{18}F-FDOPA by IDH mutation grade II and III gliomas compared with wild type. Likewise, high uptake of ^{18}F-FDOPA predicted low-growing tumors regardless of HDI status.

^{18}F-FDOPA is also used to assess the tumor response of patients with high-grade recurrent glioma treated with anti-angiogenic therapies such as bevacizumab. Absolute MTV measured 2 and 6 weeks after the start of treatment correlated with tumor response. This prediction, based on a parametric response map, showed that there was a correlation between the course and both PFS and OS.

As with ^{18}F-FDG, the results should be interpreted in conjunction with the MRI results, and ideally a blended image should be used if possible. In rare cases, ^{18}F-FDOPA may detect recurrence earlier than MRI. Inverse correlations between ^{18}F-FDOPA and ADC absorption levels and a proportional association between ^{18}F-FDOPA absorption levels and the mitotic index have been reported.

Therefore, PET ^{18}F-FDOPA can change the management of glioblastoma patients thanks to its performance in diagnosis, treatment, and prognosis assessment. The main drawbacks are its cost and availability.

4.Molecular Imaging in Pediatric Brain Tumors

Pediatric brain tumors(PBTs) include different tumor entities of different malignancies. The incidence of primary malignant and non-malignant brain tumors and other central nervous system tumors in children and adolescents in the United States is

approximately 5.67 per 100 000 person-years. In Europe, a positive trend in incidence is required until the end of the 1990s (1.7% on average per year), with an annual incidence from Europe of 6.8 per million children(0-14 years) during this period from 2000 to 2007, 15-20% of all CNS tumors were medulloblastomas. Pediatric brain tumors present a strong histological heterogeneity, and the location of the tumor is often close to important or eloquent brain structures, making complete and partial and diagnostic resection impossible(localization). Only biopsy is possible.

4.1. Imaging of amino acid metabolism in pediatric brain tumors with [^{18}F]-L-Dihydroxyphenylalanine ([^{18}F] FDOPA)

[^{18}F]-L-Dihydroxyphenylalanine ([^{18}F] FDOPA) is a large amino acid transported by neurons. The enzyme decarboxylase of the aromatic amino acid [AAAD] is involved in the metabolism of [^{18}F] FDOPA, which reaches the catecholamine storage vesicles. [^{18}F] FDOPA can cross the blood-brain barrier and is used in the brain as a precursor of dopaminergic neurotransmitters. For this reason, [^{18}F] FDOPA has been used to diagnose these neurodegenerative diseases. [^{18}F]- another hallmark of FDOPA is increased uptake into cancer cells due to overexpression of the AA transporter (mainly L-type) in certain types of tumors. [^{18}F] FDOPA can enter a variety of metabolic pathways (e.g., synthesis of peptides, proteins, purines, pyrimidines, or hormones, acting as a methyl group donor). In some types of tumors, malignant transformation increases the utilization and metabolism of amino acids as an energy source primarily used for protein synthesis and cell division, resulting in overexpression of the transport system. [^{18}F] FDOPA has shown high potential to define tumor grade and outcome of PBT. Figures 2 and 3 show an example of [^{18}F] FDOPA PET scintigraphy in a PBT patient.

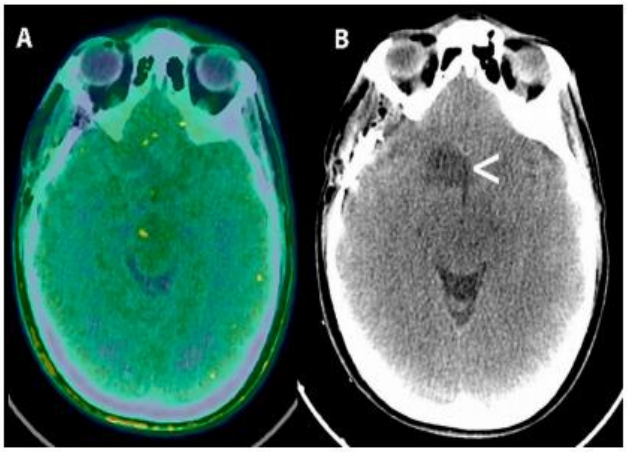

Figure 2. [^{18}F] FDOPA PET (**A**) and T2 FLAIR MRI (**B**) in a 14-year-old patient suspected of having a primary brain tumor. T2 FLAIR images showed a slight hyperintensity in the left temporal lobe(**B**,<). [^{18}F] FDOPA PET/CT scans show increased absorption of radiopharmaceuticals in lesions, with standardized absorption values of 2.2 versus 1.1 in surrounding brain tissue (**A**,<). The patient was treated surgically and subsequently diagnosed with low grade glioma (WHO grade II).

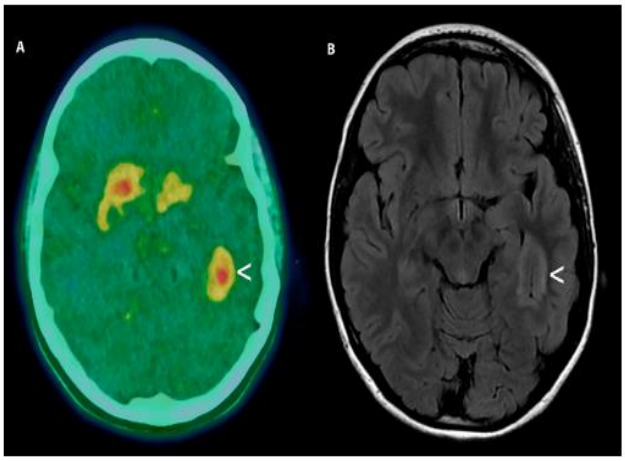

Figure 3. [^{18}F] FDOPA PET (**A**) in a 16-year-old patient who underwent surgical treatment for a hairy cell astrocytoma in september 2013 showed increased local absorption of radiopharmaceuticals. The surrounding brain tissue showed no regions (the standardized absorption value was 0.9 versus 0.8) (**A**,<). In (**B**), we report an axial CT scan showing the extent of the surgery. Regular follow-up tests in February 2019 showed negative cancer recurrence.

Morana et al. performed a comparative analysis of the diagnostic and prognostic values of [^{18}F] FDOPA PET and MR spectroscopy in PBT in 27 pediatric patients with tentative infiltrative brain lesions on conventional MRI. The authors found that absorption of [^{18}F] FDOPA was significantly associated with PFS and OS. Considering the choline/N-acetylaspartic acid ratio (Cho/NAA ratio), spectroscopy showed no significant association with prognosis. The wide distribution of institutional scans, along with radiation exposure at a relatively low cost, made MRI one of the most widely used

diagnostic tools to distinguish cerebral gliomas from non-neoplastic lesions, [^{18}F] FDOPA distinguishes between low-grade gliomas and high-grade gliomas. In another report, Morana and others. [^{18}F] it was shown that absorption of FDOPA was associated with prognosis. In this study of 26 patients with PBT, patients were examined every two weeks by MRI and [^{18}F] FDOPA PET from diffusion-weighted imaging(DWI) and arterial spin-labeled perfusion (ASL) images. [^{18}F] FDOPA uptake provided the best independent predictor of survival in multivariate analysis. By combining DWI, ASL, and [^{18}F] FDOPA PET data, the authors obtained the best predictors of tumor progression, suggesting that the combination of different diagnostic imaging methods represents the added value of malignant tumor assessment. This aspect has been further covered in another report by Morana G et al. The precision, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of [^{18}F] FDOPA PET/MRI are 93%, 89%, 100%, 100%, and 82%. Significant advances in the combination of PET and MRI data to assess the involvement of the striatum in PBT by physiological uptake of [^{18}F] FDOPA in nuclei central gray(see above), 75%, 74%, 78%, 88%, and 58% of [^{18}F] FDOPA PET/CT. Gauvain et al. have showed the safety and feasibility of PET/MRI [^{18}F] FDOPA in monitoring response to bevacizumab in the early stages of chemotherapy for recurrent PBT. The authors observed a series of responses to bevacizumab over 4 weeks, assessed by impaired absorption of [^{18}F] FDOPA. This suggests that this diagnostic imaging method can predict a response three months after the start of chemotherapy. This study requires future research on more subjects and cannot draw definitive conclusions about the role of this technique in the evaluation of response to treatment.

Chapter 2

This chapter focuses on the technical aspects of PET imaging, standards/guidelines to assist nuclear medicine professionals in recommending, performing, interpreting, and reporting the results of PET imaging of the brain in glioma patients and in overall survival progression-free survival in patients with primary brain tumors after treatment, based on preferred tumor location relative to ^{18}F-FDOPA uptake for low-grade gliomas.

1. Description of PET-DOPA imaging techniques in patients with primary brain tumors

A. PET systems provide static, dynamic, or controlled images of the distribution of positron-emitting radionuclides in the body by detecting pairs of photons that collapse due to the annihilation of a positron and an electron. The PET images are generated by a reconstruction process using the data from the match pair.

B. PET is often combined with computed tomography(CT) in a single system (PET/CT). Combined PET/MRI systems are also available for clinical use, but are currently less common.

C. Nuclear medicine computer systems and software applications collect, quantify, analyse, and display image information.

2.Common clinical indications

Common indications for PET imaging for gliomas are as follows:

1. At initial diagnosis

(a) Differentiation of grade III and IV tumors from non-neoplastic lesions or grade I and II gliomas

(b) Gliomas prognosis

(c) Definition of the optimal biopsy site(for example, site of maximum marker uptake)

(d) Delimitation of the tumor extension for surgical and radiotherapy planning

2. Diagnosis of tumor recurrence

(a) Differentiation of glioma recurrence from treatment-related changes, e.g. pseudoprogression, radionecrosis

3. Disease and therapy monitoring

(a) Evidence of malignant transformation in grade I and II gliomas

(b) Evaluation of the response during and after radiotherapy and/or chemotherapy

(c) Differentiation of tumor response from pseudo-response during antiangiogenic therapy

3.Analysis

FDOPA-PET can distinguish recurrent brain metastases from radiation-induced changes with high sensitivity and specificity(81% and 84%, respectively). Another study reported 91% accuracy in distinguishing radiation-induced changes from progression of brain metastases after radiosurgery for FDOPA-PET, exceeding MRI perfusion parameters 91% - 76%.

A three-compartment model could describe the kinetics of ^{18}F-DOPA in brain tumors(BT); compared to the cerebellum and the striatum, the brain tumor showed a higher rate of transport and uptake, which is related to the grade of the tumor. The transport rate and uptake of the marker is higher in high-grade gliomas compared to low-grade gliomas, as shown by earlier uptake in high-grade tumors (12.7 min) compared to low-grade tumors (15.7 min). In addition, high-grade gliomas are characterized by a slight washout of the marker compared to low-grade gliomas, which is likely due to a rupture of the BBB, although there is no association between contrast enhancement on magnetic resonance imaging and ^{18}F-DOPA uptake was found.

Tumor cells can upregulate the amino acid transporter and develop overexpression of protein synthesis as a marker for tumor growth and vitality; for these reasons, ^{18}F-DOPA has been proposed in recent years to characterize primary brain lesions, particularly due to high uptake in tumors versus very low uptake in normal brain tissue, with the exception of the basal ganglia.

^{18}F-FDOPA PET of previously untreated gliomas provides potentially useful non-invasive predictions of tumor grade and proliferative activity, although it does not provide similar information for previously treated gliomas. The correlation between amino acid uptake and tumor growth makes it possible to consider this tracer as

feasible for the detection or definition of tumor lesions. In a recent study by Fueger et al. 49 patients were examined with ^{18}F-DOPA PET; 22 of them had newly diagnosed glioma and the results of the images were correlated with the histological examination. ^{18}F-DOPA-PET showed a sensitivity and specificity of 85 and 89% for the detection of primary tumors, representing an additional potential application as a predictor of tumor grade and proliferation with significant prognostic value. These potential applications of ^{18}F-DOPA PET and PET/CT imaging, while encouraging, have been confirmed by a small number of previous publications. In particular, Schiepers et al. examined 33 patients with primary brain lesions in a paper that focused on investigating the kinetics of ^{18}F-DOPA in primary and recurrent brain tumors and metastatic lesions. The researchers evaluated the kinetics of ^{18}F-DOPA uptake using dynamic PET images captured for 75 minutes immediately after ^{18}F-DOPA injection. Their results suggested that, unlike the striatum,^{18}F-DOPA is transported but not locked up in tumors. Furthermore, the uptake curve could be related to the grade of the tumor; in fact, high-grade tumors showed a strongly descending branch after an early peak, while the time/activity curve for low-grade tumors was slightly skewed. This fact could indicate the possible use of ^{18}F-DOPA-PET in the differential diagnosis and classification of brain lesions. Although Schiepers et al. proposed different acquisition protocols for the studies, other researchers have directed their attention to this area using the common acquisition protocol, taking into account 10-30 minutes after injection of the window of highest tracer uptake; in the work of Fueger et al. the differential diagnosis was made with the semi-quantitative analysis of the standardized maximum intake value (SUVmax).

SUVmax is a semi-quantitative parameter of the radiotracer uptake, measured according to the following formula:

$$SUV=\frac{\text{Radioactivity(kBq)/tissue volume(ml)}}{\text{Injected dose(kBg)/body weight(g)}}$$

An SUVmax threshold of 2.72 well distinguished low-grade from high-grade tumors. Semi-quantitative analysis by measuring SUVmax or other numerical parameters cited below makes it possible to compare the diagnostic performance of ^{18}F-DOPA-PET with

the precision of other tracers currently used in the diagnosis of brain tumors, such as ^{18}F-FDG, amino acid tracers and nucleoside tracer DNA synthesis.

Compared to ^{18}F-FDG, ^{18}F-DOPA-PET was tested in a population of 81 patients using the standard single capture protocol: although the SUVmax of ^{18}F-DOPA was less than that of ^{18}F-FDG, the amino acid tracer, in the low-grade tumors studied showed greater precision with higher sensitivity and similar specificity, allowing excellent visualization of high- and low-grade tumors. In particular, tumor diagnosis was provided by defining the relationship between tumor uptake and normal hemispherical tissue uptake (T/N) and measuring the ratios of tumor uptake to striatum uptake. Another interesting article by Becherer et al. compared PET/CT with ^{18}F-DOPA and with ^{11}C-MET in the assessment of the brain tumor: Of the 22 patients examined, 18 had a primary brain tumor. The diagnostic precision of both tracers in measuring SUVmax in lesions and in the relationship between tumor and contralateral hemisphere was similar: the SUVmax tumor/contralateral aspect ratios were 2.05 ± 0.91 for ^{11}C-MET and 2.04 ± 0.53 respectively for ^{18}F-DOPA. Researchers emphasized the effectiveness of ^{18}F-DOPA as a tracer with the physical benefits of fluorine-18 and the pharmacological properties of methionine useful for brain tumor imaging. On the contrary, it is important to emphasize that a benign lesion that was later diagnosed as focal demyelination on histological examination gave false positive results showing increased uptake of both ^{18}F-DOPA and ^{11}C-MET.

The potential role of ^{18}F-DOPA PET/CT in tumor imaging is determined by further research by Tripathi et al. In this study, 13 patients with primary or recurrent tumors were tested on three tracers: ^{18}F-DOPA, ^{18}F-FDG and [^{18}F]fluorothymidine (^{18}F-FLT). The absorptions of the three tracers were analyzed visually and the SUVmax and T/N ratios were calculated. The SUV ratio (SUVr) was calculated by the following formula: SUVr = SUVmax/SUVmax occ.

^{18}F-DOPA was diagnosed as a tumor in 13/13 cases, ^{18}F-FDG PET/CT was positive in 7 of 13 cases and ^{18}F-FLT was positive in 4 of 13 cases. Again, in this article, the T/N ratio was favorable for ^{18}F-DOPA (2.3 ± 0.51) compared to ^{18}F-FLT (1.8 ± 0.91) despite a higher SUV value of the observed lesions with ^{18}F-FDG (1.03 ± 0.64).

The combination of PET with CT in hybrid devices has several advantages for the patient. Attenuation correction data derived from an actual cesium or germanium source PET is replaced with data from a low energy X-ray photon source, which enables more accurate quantification of functional data and a fusion of functional information and anatomical data. In addition, the latest generation of helical PET/CT scanners enables very fast acquisition studies even after intravenous contrast agent administration (both in the arterial and in the venous phase).

It is important to note that while ^{18}F-DOPA PET and PET/CT are promising diagnostic tools in the detection of primary brain lesions, particularly with regard to histological examination, diagnostic precision must be matched with the best diagnostic option in management of the brain tumor patients are compared, which is an MRI. To the best of our knowledge, only one article has focused on the comparative evaluation of PET and MRI with ^{18}F-DOPA. Ledezma et al. examined a population of 91 patients: 21 with a later surgically confirmed tumor and 70 with a pathological diagnosis of glioma but without additional pathological follow-up. For this purpose, ^{18}F-DOPA PET/CT and MRI were combined, analyzed for concordance and correlated with histopathological data. Of 21 patients, ^{18}F-DOPA scans were positive in 9 of 10 previously unresected tumors (90%) and 11/11 (100%) recurrent tumors. Of the other 70 glioma patients, 49/54 (90%) patients were found to have a match between MRI and PET with adequate follow-up, and in some cases an ^{18}F-DOPA scan preceded the tumor diagnosis on MRI. In contrast to the results of other cited studies, ^{18}F-DOPA uptake in this article was not associated with tumor classification. The researchers concluded that the ^{18}F-DOPA-PET/MRI fusion could provide better anatomical localization of the tracer uptake and, consequently, the pathology and, in a minority of cases, take advantage of the added value of metabolic characterization by removing non-tumors, visible in the MRI.

The main biological processes involved in primary brain tumor recurrence are angiogenesis and local invasion; in addition, it was recently discovered that the brain tumor displaces the stem cells responsible for self-renewal, the ability to initiate the brain tumor after orthotopic implantation in xenografts, and multipotency.

The use of ^{18}F-DOPA in diagnosing recurrence of brain tumors is still a largely unexplored area. Chen et al. examined the possible role of ^{18}F-DOPA-PET in differentiating between recurrent neoplasia and radiation necrosis in a group of patients with suspected recurrent brain tumor and compared it to ^{18}F-FDG. Although the number of patients studied was small (four treated with radiation therapy: three with metastatic cancer and one with grade III glioma), ^{18}F-FDG gave false negative results and ^{18}F-DOPA correctly identified a recurrent tumor; the remaining three patients with no active disease or radiation necrosis in long-term remission had no visible ^{18}F-DOPA uptake.

A study cited by Tripathi et al. ^{18}F-FDG, ^{18}F-FLT and ^{18}F-DOPA were compared in the assessment of primary brain tumors and recurrent low-grade gliomas, and in a population of 15 patients tested, ^{18}F-DOPA was the other in brain detection diagnosis of tumors and local recurrences which were shown to be superior to the two tracers. Important suggestions can be provided by Ledezma et al. it has been shown that ^{18}F-DOPA can identify residual tumors which are not clearly visible on MRI alone. In only one case, ^{18}F-DOPA showed pathological uptake in the area surrounding the intervention site, while MRI showed tumors at the site before ^{18}F-DOPA uptake only during follow-up after 3 months. This fact suggests that uptake of ^{18}F-DOPA may detect residual/recurrent tumors that are not clearly defined by MRI alone. In our experience, we have observed the good feasibility of ^{18}F-DOPA as a tracer for detecting recurrence of brain tumors compared to histological examination, but preliminary data are still important for statistical analysis, not suitable. ^{18}F-DOPA is excellent in detecting local recurrence due to its unique property of being an amino acid tracer and its low physiological absorption in normal white and gray matter, except in case of basal ganglia, it should show the possibility. Unfortunately, the assessment of this aspect is still limited in the literature. Report on the role of ^{18}F-DOPA imaging (which may require surgical resection or biopsy on a case-by-case basis to establish the true pathogenesis of imaging changes) and ^{11}C-MET and other radiolabeled amino acids non-tumor uptake, as has been done. In fact, if amino acid uptake in inflammatory processes that characterize ischemic areas of the brain, infarcts, scar tissue, abscesses,

irradiated areas and many other non-neoplastic processes is lower than FDG uptake, this can lead to possible errors, especially after chemotherapy and radiation therapy.

Finally, it is important to highlight the potential benefit in this area of the clinical availability of newer and more efficient PET/CT and hybrid PET/MRI scanners. A baseline MRI could help delineate the area of interest and evaluate PET images based on MRI abnormalities. In an initial experience and a comparison with PET/CT in intracranial masses, the PET data sets showed a diagnostic image quality similar to the hybrid PET/MR and PET/CT studies; therefore, it is possible to obtain structural, functional and molecular images in patients with brain tumors with hybrid PET/MR imaging. In any case, it is necessary to delve into the possible relationship of false positives or traps in benign disease that has already been described using ^{11}C-MET and the same ^{18}F-DOPA in one patient with localized demyelination.

4.Overall progression-free survival in patients with primary brain tumors after treatment: Is PET [^{18}F] FDOPA a prognostic factor in these patients?

The aim was to study progression-free survival (PFS) and overall survival (OS) in a population affected by primary brain tumors (PBT) as assessed by [^{18}F]L-dihydroxyphenylalanine ([^{18}F]FDOPA) positron emission tomography/computed tomography (PET)/CT). Current treatment for primary brain tumors (PBT) is based on a multimodal intervention that combines surgery, radiation therapy, and/or chemotherapy and to monitor, in fact, magnetic resonance imaging(MRI) is the modality of choice for the detection of recurrent tumors. MRI enables accurate morphological assessment of the brain and its ability to detect contrast-enhanced pathological areas, a feature of recurrence in previously surgically primary brain tumors. However, even with MRI, proper assessment of treatment-induced changes or the possibility of tumor recurrence is not readily discernible; Furthermore, it was recently reported that the assessment of primary brain tumors by MRI significantly underestimated tumor volume, especially for low-grade tumors due to lack of contrast enhancement. Positron emission tomography/computed tomography (PET/CT) with

amino [18F] L-dihydroxyphenylalanine ([18F] FDOPA) has shown to be a promising diagnostic tool in the assessment of primary recurrence of brain tumors with in vivo detection of amino acid metabolism and sensitivity and specificity compared with MRI. The classification of primary brain tumors was significantly revised in 2016, with the use of molecular and histological parameters to define the major tumor types. For the first time, genetically determined entities are now included in the classification of diffuse glioma, myeloblastoma, and embryonal tumor as for other histological variants of primary brain tumors. However, the tumor grade as defined by the World Health Organization (WHO) is still a marker of tumor classification, with younger age, activity status and resection level being among the most important factors, the most important prognostic factor in primary brain tumors. In particular, a lower age at diagnosis (<50 years) was associated with a better prognosis, while a higher functional impairment demonstrated by Karnofsky Performance Status (KPS) and residual tumor volume are important negative prognostic factors. The purpose is to investigate the potential predictive role of [18F] FDOPA PET/CT in a cohort of patients previously treated for primary brain tumor, including II, III and IV WHO.

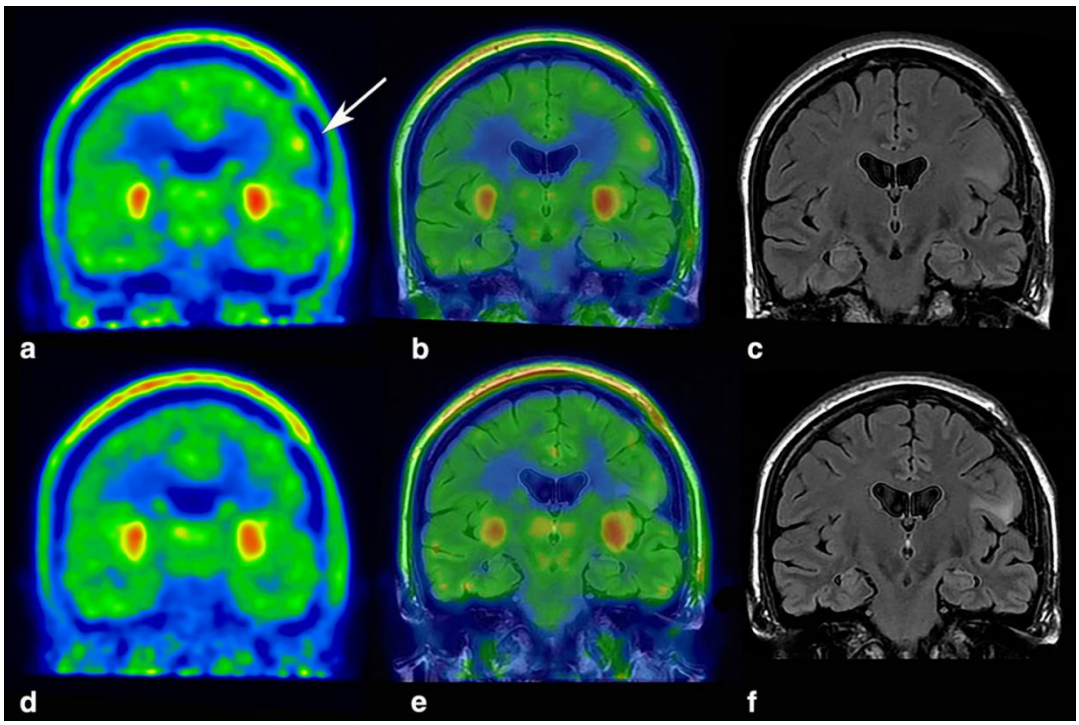

Figure 1. a Coronal view of the [18F] FDOPA scan in a person with primary brain tumor grade II. It shows the focal area (arrow) with increased uptake of radiolabeled compounds in the left frontal lobe of the surgical margin. The SUVr was equal to 1.17. In **b**, we report on PET / MRI fusion imaging, and in **c**, we

report on T2-emphasized MRI. A 19-month follow-up scan showed successful uptake of radiolabeled compounds at the same site (**d**). No additional processing was performed between scans. **e** reports on PET / MRI fusion imaging, and **f** reports on T2-emphasized MRI.

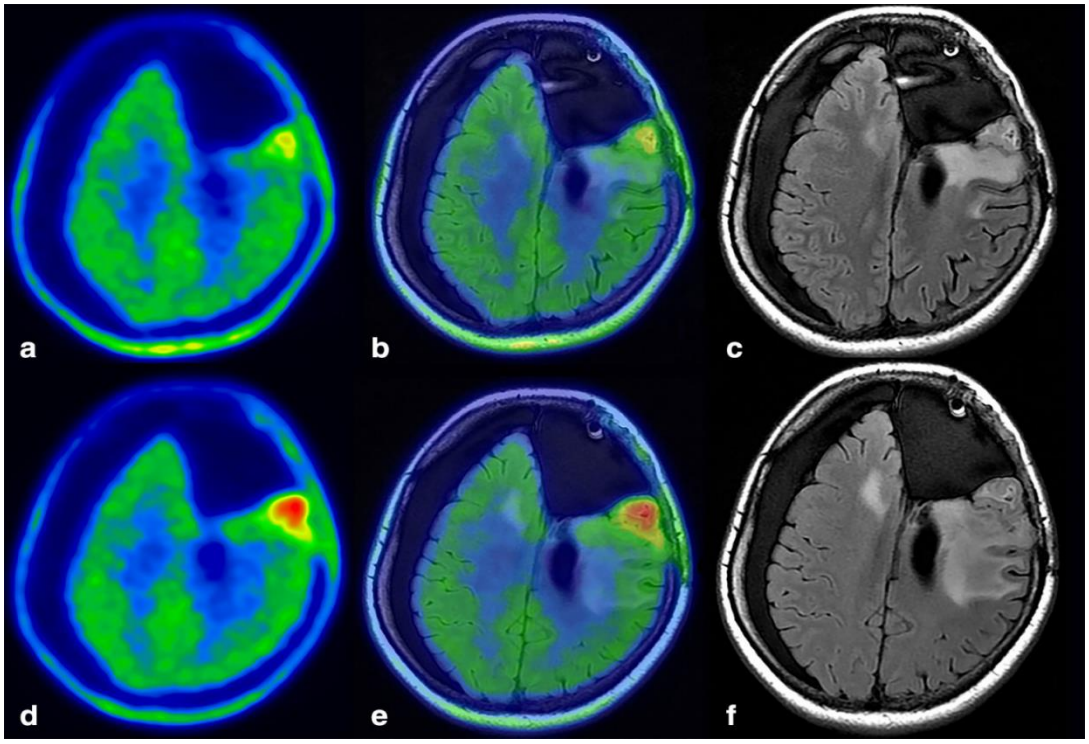

Figure 2. a Axial cross-section showing increased [^{18}F] FDOPA uptake in the rest of the frontal lobe after surgery in a Grade III glioma patient (SUVr = 1.45) 6 months after surgery. In **b**, we report on PET / MRI fusion imaging, and in **c**, we report on T2-emphasized MRI. A 13-month follow-up of **d** shows disease progression with a further increase in [^{18}F] FDOPA uptake (SUVr = 1.7). **e** reports on PET / MRI fusion imaging, and **f** reports on T2-emphasized MRI.

5.Preferred tumor location for ^{18}F-FDOPA uptake in low-grade gliomas

Tumor localization and 3,4-dihydroxy-6-18F-fluor-L phenylalanine (FDOPA) uptake may be associated, but low-grade gliomas (LGGs), the preferred tumor location for FDOPA uptake remains to be investigated. The purpose of this section of this chapter was to use a stochastic X-ray atlas to identify differences in the frequency of tumor localization between hypometabolized and hypermetabolized LGGs in FDOPA.

5.1. Tumor Location Overview

Tumor location correlates with demographics, molecular status, clinical manifestations, surgical management, and survival, making it an important factor in the care of patients with low-grade glioma (LGG) is. For example, LGG is more likely to penetrate the insula in older patients than in younger patients who tend to be located in the temporal lobe. From a molecular point of view, only 20% of isocitrate dehydrogenase (IDH) wild-

type gliomas were located in the frontal lobe, whereas IDH mutant LGGs, especially those with 1p19q co-deletion, could occur in the frontal lobe. Frontal lobe LGG was associated with an increased risk of preoperative seizure episodes. In terms of surgery, LGG in the insular area had a poorer prognosis with less resection, but patients with frontal lobe LGG had a better complete resection and prognosis than patients with other lobe LGG. To assess tumor distribution, brain atlas based on probabilistic magnetic resonance imaging (MRI) was used in several studies to determine patient characteristics (age and gender), clinical appearance (symptoms and Karnofsky's), we evaluated the potential location of anatomical tumors related to performance, and molecular status (IDH, epidermal growth factor receptor, O6 methylguanine methyltransferase and phosphatase and tensin homolog). Amino acid positron emission tomography (PET), including 3,4dihydroxy-6-18F-fluor-Lphenylalanine (FDOPA), is widely used as a clinical tool in neuro-oncology to identify metabolically active tumor tissues. Higher intake of amino acid tracers has been reported to result in higher tumor grades and shorter overall or progression-free survival. Molecular states such as IDH mutations and deletion of the 1p19q code are still under discussion, but may be related to the uptake of amino acid tracers. Tumor location and FDOPA uptake are related and may co-influence the prognosis of patients with LGG. However, favorable tumor locations that correlate with the uptake of various FDOPAs have not yet been investigated. The purpose of this study was to identify differences in the frequency of localization between hypometabolized and hypermetabolized FDOPA LGGs using stochastic MRI-based brain atlas to determine overall survival (OS) in different FDOPA metabolic states to evaluate. Depiction of such spatial patterns can improve the understanding of the pathophysiology of the underlying tumor and may lead to appropriate subsequent treatment. MNI template Tumor ROI overlays from hypometabolized or hypermetabolized LGGs on the brain showed a high number of hypometabolized FDOPA LGGs located in the frontal lobe (Figure. 3a). During that time, numerous FDOPA-hypermetabolized LGGs were found in the insula, putamen, and temporal lobe (Fig. 3b). LGG's ADIFFI statistical analysis based on FDOPA metabolic status identified two spatially distinct clusters. One was located in the frontal

lobe, especially in the superior frontal gyrus, and was often associated with FDOPA's hypometabolized LGG (Fig. 4a) and others of were more frequently localized to the insula in association with FDOPA hypermetabolism LGG (Fig. 4b). In short, LGG in young patients (<52 years) is preferably localized in the frontal lobe (particularly the superior frontal gyrus and triangular to orbital) and temporal lobe (particularly the fusiform gyrus). LGG in elderly patients (aged 52 and over) did not have a favorable location. LGG with low FLAIR volume (<29 ml) or BTV (<0.22 ml) did not show favorable localization. There was no preferred position between two pairs with different molecular states of IDH / 1p19q. The Kaplan-Meier curve and Log-rank test showed a significant difference in OS between hypometabolized and hypermetabolized FDOPA LGG (Fig. 5, p = .046), indicating a longer survival of hypometabolized FDOPA LGG. Univariate analysis with Cox showed a significant increase in patient age-related risk (hazard ratio [HR] = 1.075, 95% CI = [1.003, 1.152], p = 0.042), whereas nSUVmax not so (nSUVmax (HR = 1.403, 95% CI = [0.670, 2.937], p = 0.37), FLAIR volume (HR = 0.997, 95% CI = [0.977, 1.017], p = 0.74) or BTV (HR) = 1.056, 95% CI = [0.991, 1.125], p = 0.089).

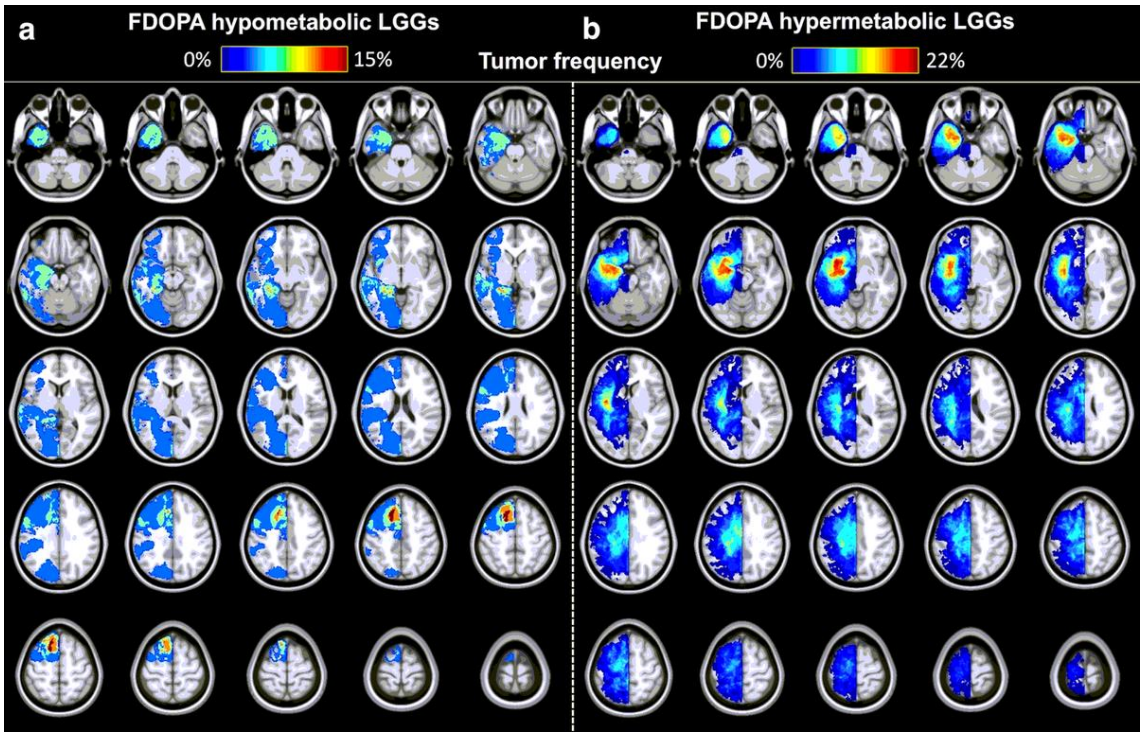

Figure 3. Frequency of tumor development with FDOPA hypometabolism per voxel (n = 14, nSUVmax <1) and hypermetabolism LGGs (n = 37, nSUVmax >1). a) Frequency of tumor development in patients with FDOPA hypometabolism LGG. b) Frequency of tumor development in patients with FDOPA hypermetabolism LGG. Note: All ROIs in the left hemisphere are mirrored in the right hemisphere.

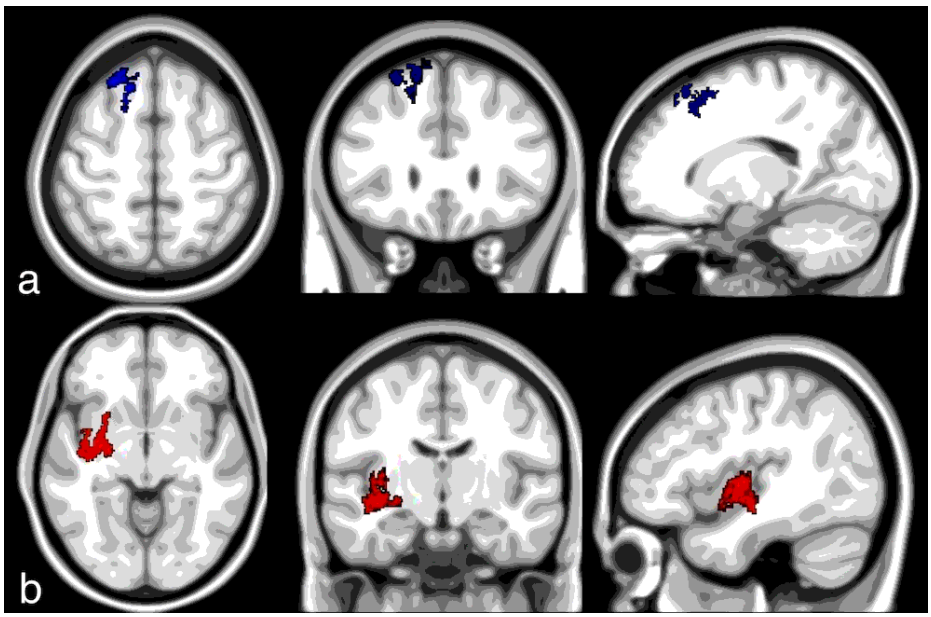

Figure 4. Frequency of voxel-specific tumorigenesis of hypometabolized FDOPA (n = 14, nSUVmax <1) and hypermetabolism LGG (n = 37, nSUVmax > 1). a) Frequency of tumor development in patients with FDOPA hypometabolism LGG. b) Frequency of tumor development in patients with FDOPA hypermetabolism LGG. Note: All ROIs in the left hemisphere are mirrored in the right hemisphere.

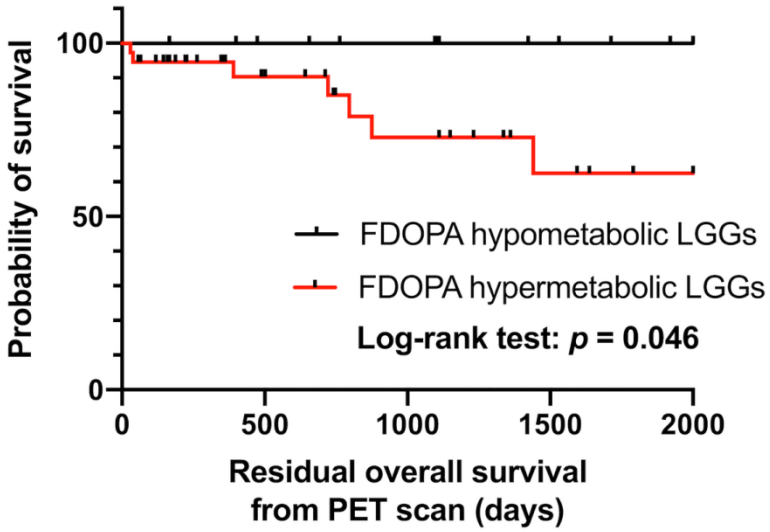

Figure 5. Kaplan-Meier plots and logrank tests show that there is a significant difference in overall survival between hypometabolized and hypermetabolized LGGs in FDOPA.

Chapter 3

The purpose of this chapter is to assess the value of diagnostic imaging in patients with brain tumors. This can be improved if pathological data can be estimated from the image input using a predictive model. The purpose is also to compare the diagnostic information obtained with 6-[^{18}F] fluoro-L 3,4 dihydroxyphenylalanine (F-DOPA) PET with the relative cerebral blood volume (rCBV) map of recurrent or progressive glioma.

1. Testing Procedures / Specifications

Inquiries

Employees of a nuclear medicine diagnostic imaging facility should check with the nuclear pharmacy provider for the availability of radiotracers before planning a test. Advance notice may be required for tracer delivery. Research requirements should include:

1. Appropriate clinical information about the patient and well-specified clinical questions to justify the study and enable appropriate test / study coding.
2. Information about the patient's ability to cooperate with the test and caregiver participation may be helpful.
3. Information on current medications, including glucocorticoids, for correct study interpretation and avoidance of unwanted pharmacological interactions when mild sedation is required.
4. History of previous treatments, including previous chemotherapy, surgery, and radiation therapy that may affect the distribution of radiopharmaceuticals.
5. Results of relevant imaging tests, excisions and biopsies performed, and test results.

1.1. Patient Preparation and Precautions

1. To measure a standardized intake (SUV), the patient's height and weight must be documented.
2. The latest morphological imaging with MRI (T1, T1 + contrast agent, T2 / FLAIR) should be available for image fusion.
3. Patients need to be educated on procedures to ensure optimal compliance.
4. The patient should be able to lie quietly for at least 30-40 minutes.

5. If sedation is required for FDOPA imaging, sedation should be started approximately 20-60 minutes before the examination.

6. Patients should fast before the test to ensure a stable metabolic state. At least 4 hours of acceleration is recommended for MET, FET, FDOPA, and FDG imaging.

7. Before scanning, the patient should empty the bladder to maximize comfort during the study and reduce the dose absorbed by the bladder.

8. For pregnant patients, clinical decisions must be made to weigh the benefits to the patient for possible harm.

9. FDOPA PET does not require premedication with carbidopa. Most of the previously published FDOPA-PET studies in patients with brain tumors did not use carbidopa or other inhibitors of peripheral FDOPA metabolism.

10. Patients are advised to be well hydrated and to empty their bladder frequently.

1.2. Radiopharmaceuticals

3,4 Dihydroxy 6 [^{18}F] Fluoro-L phenylalanine; Fluorodopa F18 (FDOPA)

2 Deoxy2 [^{18}F] Fluoro-D-glucose; Fludeoxyglucose F18 (FDG)

O (2 [^{18}F] Fluoroethyl) L Tyrosine (FET)

L [Methyl ^{11}C] Methionine; Methionine C11 (MET)

1.3. Radiopharmaceutical Preparation

All radiopharmaceuticals must be manufactured by qualified personnel using cGMP compliant methods that meet regulatory requirements. Radiopharmaceuticals are delivered ready to use. Quality control (QC) is performed by the manufacturer before the final product is shipped.

1.4. Adult Dosing Activities

The recommended injection activities for adult brain imaging are: ^{18}F-FDOPA: 185-200 MBq

1.5. Pediatric Management Activities

In children, the dose of radioactivity should be calculated as a percentage of the adult dose relative to the child's weight, using the coefficients provided by the EANM Pediatric Task Group. In sensitive systems, the dose can be reduced.

2. PET Acquisition Protocol

Positioning

Scans should be performed with the patient's head in a special holder and the arms along the body. The entire brain, including the entire cerebellum, should be in sight (FOV) and extreme neck extension or flexion should be avoided.

Head Stability

1. Immediately prior to a PET scan, the patient should be instructed not to move his head in any part of the examination.

2. Head stability can be achieved by placing the patient in the provided holder as completely as possible and placing the patient comfortably. Other flexible headrests, such as tapes, pads, or thermoplastic molds or vacuum mattresses for children, can be used to help plan radiation therapy.

3. Patients should be continuously visually monitored during the examination. Monitoring is especially important for patients with tumor-related seizures.

2.1. PET Imaging Sequence

The recommended PET imaging sequences are:

1. PET / CT scout topogram for setting the CT field of view.

2. Attenuation correction requires a low-dose CT scan, an MRI scan for attenuation correction, or a transmission scan. Do not use mathematical attenuation correction (ie, based on the patient's outer contour (derived from PET images without attenuation correction).

3. Static or dynamic PET acquisition in a single field of view.

2.2. PET image re-image Configuration

1. All corrections for quantitative interpretation are required during image reconstruction, including attenuation, scatter, random, dead time, attenuation correction, and detector sensitivity normalization.

2. Flight time acquisition and reconstruction is permitted, but the benefits of brain imaging have not yet been fully investigated.

3. Iterative reconstruction is a field standard and should be used. However, if the iterative reconstruction leads to upward distortion due to the non-negative constraints

applied during the reconstruction, a filtered back-projection reconstruction can be used as an alternative.

4. Using resolution modeling during a reconstruction called the Point Spread Function (PSF) reconstruction can result in Gibbs artifacts and quantitative errors and is not recommended.

5. The following reconfiguration settings / protocols are recommended to harmonize PET image quality:

(a) One of the reconstructions is that the reconstructed image meets the EARL requirements for image quality restoration, which allows PET data to be used in multi-facility settings or reference datasets.

(b) Higher resolution reconstruction is desired for visual interpretation of tumor boundaries, as the above harmonized reconstruction settings guarantee equivalent image quality between different generations of PET / CT systems. If multiple reconstructions are available for a particular PET system, a high resolution, dedicated protocol can be applied to the brain reconstruction. Such a protocol should meet the following requirements:

- Voxel size 1-2 mm, but <3 mm in each direction
- Reconstructed spatial resolution half width <6 mm

2.3. Interpretation / Quantification

Recorded values and standardized calculations (SUV) of image analysis

2.3.1. Typical Image Display

1. PET images require at least 16-bit pixels to provide a reasonable range of values, and image display must use proper image scaling. Color scales can be used. PET images should be displayed in the longitudinal direction and further correlated with coronal and sagittal morphological images.

2. Internal landmarks can be used to orient for a standardized image display. A reorientation procedure based on the commissure line is often used.

3. FDOPA: When the display scale is colored, the background radioactivity of a healthy brain is in the lower third of the range (blue on the widely used Sokoloff scale) to create

standardized visual conditions and detection of increased tracer accumulation in the background.

2.4. Static FDOPA PET

1. SUV calculation is optional and can be performed by dividing the radioactivity concentration in the tissue (kilobecquerel per milliliter) by the infused radioactivity (megabecquerel) per body weight (kilogram) with volume of distribution corresponding to the tracer.

2. Standard total image of the area defined in the comparability section of PET (Points 1, 2, and 3 are used for clinical reading and are enrolled with new high resolution contrast-enhanced T1-weighted images that must be merged.

3. In the first visual analysis, a qualitative assessment can be made, and if tracer uptake visually exceeds the background activity of the contralateral cortex, the lesion of interest is classified as positive and uptake is increased. If is not seen, it is classified as negative.

4. FDOPA: Semi-quantitative measurements of mean and maximum tumor activity uptake calculated as a ratio associated with a seemingly healthy striatum on the opposite side of the tumor (tumor-striatum ratio, TSRmean or TSRmax). The striatum is the most commonly used reference area. Other reference areas were not systematically investigated.

2.5. Limit value for determining biological tumor volume

FDOPA: SUV (not histologically validated) larger than the average of healthy striatum

2.6. Interpretation of static FDOPA PET data

Based on the WHO 2016 classification, gliomas are gradually classified based on histological and molecular characteristics and are no longer low-grade or high-grade gliomas as follows:

1. Astrocytoma grades II and III (including isocitrate dehydrogenase 1 (IDH1) mutation, 1p / 19q without codeletion)
2. Oligodendrocyte gliomas grade II and III (with IDH1 mutation, 1p / 19q with codeletion)
3. Wild-type astrocytoma or oligodendrocyte glioma not specified
4. Secondary glioma (with IDH1 mutation)

5. Primary glioma (IDH1 wild-type or IDH1 negative)

3.Physiological tracer distribution of FDOPA

1. General: Moderately increased uptake into basal ganglia and pituitary gland, cerebral, skin, optic nerve, ocular muscle and salivary gland.

2. Unusual: Pineal gland.

3. There is no increase in uptake into the vascular structure.

3.1. Known pitfalls

Included in all tracers of FDOPA

1. Inflammatory lesions and seizures can increase uptake.

2. For small lesions, uptake may be underestimated compared to image resolution.

4.Documentation and Reporting

The content of the report is a legal document related to patient management and clinical outcomes. Whenever possible, it is advisable to provide a structured report with a concise final statement designed to answer a particular clinical question. Regardless of the radiotracer, the report should follow the following general structure:

4.1. General Information

1. Other identifiers such as patient name and date of birth.

2. The name of the referral doctor.

3. Test type and date.

4. Radiopharmaceutical containing the route of administration and the amount of activity administered.

5. Medical history of a patient focused on diagnosis and tumor-related treatment, and clinical issues that led to its application to the study.

4.2. Report Body

1. Process Description

(a) Information about the imaging process (such as static or dynamic scanning) and the time from PET tracer injection to image acquisition.

(b) Blood glucose level measured at the time of injection when using FDG.

(c) If sedatives are being administered, the type and timing of medication associated with the tracer injection.

(d) If a low-dose CT scan is performed to compensate for attenuation, notes such as "Not performed for diagnostic purposes, not a substitute for diagnostic CT" may be added.

(e) The use of non-traditional systems (PET / MRI, etc.) should be mentioned.

2. Data quality

(a) Abnormal tracer biodistribution

(b) CT-related artifacts (such as metal implants).

(c) Insufficient adherence to fasting.

(d) Observed events that may affect interpretation as head movements, seizure activity.

(e) With FDG, blood sugar levels rise.

3. Comparison data

(a) Wherever possible, PET images should be compared with morphological data, especially MRI data.

(b) PET images should be compared to previous PET scans to assess disease progression. (c) Before explaining the image findings, it is necessary to record the type and date of the comparison data.

4. Explanation of findings

(a) Normality of radiotracer uptake should be reported, normal or abnormal.

(b) In case of abnormalities, the location, extent, and intensity of pathological tracer accumulation associated with normal tissue uptake (with correct anatomical description) should be explained.

(c) Recording intake characteristics including:

-Intake shape, eg focal, diffuse, non-uniform.

-Absorption intensity (light, moderate, or strong) associated with healthy absorption into the brain.

-Range and peak capture. For example, it correlates with T1 contrast enhancement on MRI and / or overt anatomical abnormalities on T2 / FLAIR hyperintensity or CT / low-dose CT images.

(d) Semi-quantitative parameter

-FDOPA determination SUV / SUV ratio

(e) Clinically relevant contingent findings should be reported as extracerebral metastasis for example.

(f) Comparison with PET studies conducted prior to, such as therapeutic response or malignant transformation.

4.3. Interpretation: The interpretation should address the questions posed in the clinical study, taking into account medical history, comparative images, and restrictions. If possible, an accurate diagnosis should be made. Additional scans or follow-up scans are recommended as needed.

5. Device specifications

5.1. System Specifications

We recommend using the latest 3D PET / CT system. The system should be able to collect low-dose CT images that can be used to attenuate and correction for the scattering of PET emission data. You can use a special PET-only system for the brain. However, if equipped with a transparent scan source of sufficient strength recommended by the manufacturer, ensure sufficient quality of the transparent scan and compensate for the attenuation of PET emission data. The PET (/ CT) system must have a minimum axial visual field of 15 cm for proper coverage of the entire brain, including the cerebellum and brain stem.

5.2. The PET acquisition

System must be able to acquire PET emission data in both static and dynamic, or list mode, in 3D mode. The data should be reconstructed online or offline (that is, retroactively) in one or more frames, as indicated in the research protocol and these guidelines. In addition, you should be able to reconstruct the PET image with or without attenuation correction. PET images without attenuation compensation should not be used for primary interpretation. However, it does help detect attenuation artifacts in attenuation-corrected PET images. The system includes, but is not limited to, online randomization correction, scattering correction, attenuation correction, dead time correction, attenuation(decay) and frequency correction, normalization

(correction), and all necessary for quantitative PET imaging and reconstruction of the brain. It must have features and methods for detectors sensitivity.

5.3. Quality Control and Improvement

PET System Quality Control and Performance Harmony Between Institutions

Regularly check PET system performance through several QC experiments to ensure adequate image quality, quantitative performance and image harmony is needed.

All regular and vendor-provided maintenance and QC procedures must be followed. In a QC experiment, you should at least address the following: ◎

- Daily verification of detector performance, that is it features a point, rod, or cylindrical light source for automatically testing and visualizing the proper functioning of the detector module, including 2D sinogram inspection. ◎
- Daily verification of calibration of PET activity concentration measurements using a cylindrical phantom source filled with activity according to the manufacturer's recommended procedure. ◎
- Mutual calibration of PET (/ CT) systems using locally used dose calibrators to prepare and measure patient-specific radiotracer activity. Mutual calibration should be performed according to EARL recommendations and standards. ◎
- The correct alignment of PET and CT should be confirmed according to the manufacturer's recommended procedure and frequency. ◎
- Additional QC procedures are performed less frequently according to the manufacturer's instructions and EANM's recommendations for routine QC of nuclear medicine equipment.

6. Volumetric assessment of recurrent or progressive glioma: Comparison of FDOPA-PET and perfusion-enhanced MRI

This study was conducted in the brain relative to 6 [^{18}F] fluoro-L-3,4 dihydroxyphenylalanine (FDOPA-PET) and blood volume (rCBV) used to compare the diagnostic information obtained. Map of a large, unselected patient population with recurrent or progressive glioma. The focus is on volume comparison and spatial concordance analysis.

6.1. Comparative volume assessment

The intersection between the tumor VOI and the rCBV map defined in the comparative volume assessment PET image was calculated using PMOD. Spatial congruence was defined as the percentage of total tumor volume that overlapped between the two series of studies. In this analysis, the total tumor volume was defined as: $FDOPA_{vol\ 1.6}$ + $rCBV_{vol\ 1.6}$-O_{vol}, where $FDOPA_{vol\ 1.6}$ and $rCBV_{vol\ 1.6}$ are the pathological signal volumes identified by each modality, O_{vol} is the overlapping volume. Hotspots related to FDOPA uptake and rCBV were placed semi-automatically and the distance between them was calculated. As mentioned earlier, we defined tumor and reference VOI in morphological MR images to compare tumor and background contrast using various functional parameters. Tumor VOI was defined as a signal change in morphological MR images. For contrast-enhanced tumors (n = 40), tumor volume was determined on the ce-T1-W image using a visually determined cutoff. For non-concentrated tumors (n = 10), a 10 cm^3 spherical VOI was placed at the center of the signal anomalies on T1-weighted and T2-weighted images. Large reference VOIs were placed in the contralateral hemisphere of areas of normal-looking brain tissue, including white and gray matter. These VOIs were transferred to a co-registered rCBV map and PET scan, and TBR was calculated by dividing the mean of each parameter of tumor VOI by the corresponding mean of normal brain VOI. A raw histogram of tumor VOI and reference VOI was provided for each diagnostic imaging method. The maximum pixel value within the tumor VOI was determined and the raw histogram was normalized to one unit of standardized bin width and line integral.

6.2. Analysis

High-grade gliomas showed significantly higher $FDOPA_{vol\ 1.6}$ than low-grade gliomas (median $FDOPA_{vol\ 1.6}$ 18.69 ml and 4.81 ml, high-grade and low-grade gliomas, only a tendency towards p = 0.023), $rCBV_{vol\ 1.6}$ the significance was observed (median high- and low-grade gliomas $rCBV_{vol\ 1.6}$ 1.61 ml and 0.5 ml, p = 0.071). The median tumor volume was 12.26 ml (18.75 and 4.81 for high-grade and low-grade gliomas, p = 0.019). The contributions to total tumor volume were 89.95% and 5.61% for FDOPA uptake and rCBV (Fig. 1). The median O_{vol} was 0.28 ml for the entire population (0.49 ml and 0 ml

for high-grade and low-grade gliomas, p = 0.025). This resulted in a spatial congruence of the overall median of 1.38% (range 0-39.22%). There was no significant difference in spatial agreement between high-grade gliomas and low-grade gliomas (p = 0.061). Table 1 summarizes the results of the comparative volume evaluation.

6.2.1. The tumor brain ratio

TBR was significantly higher in the FDOPA-PET study than in the rCBV study (total mean TBR 1.76 ± 0.60 and 1.15 ± 0.52 of FDOPA uptake and rCBV, p< 0.0001; Figure 2). There was no difference in TBR between high-grade gliomas and low-grade gliomas (p = 0.36 and p = 0.09 for rCBV and FDOPA uptake, respectively).

6.2.2. Histogram comparison

The histogram of the FDOPA intake recording provided a clear image of tumor's separation from background, while it is based on rCBV histogram that is poor (Figure 3).

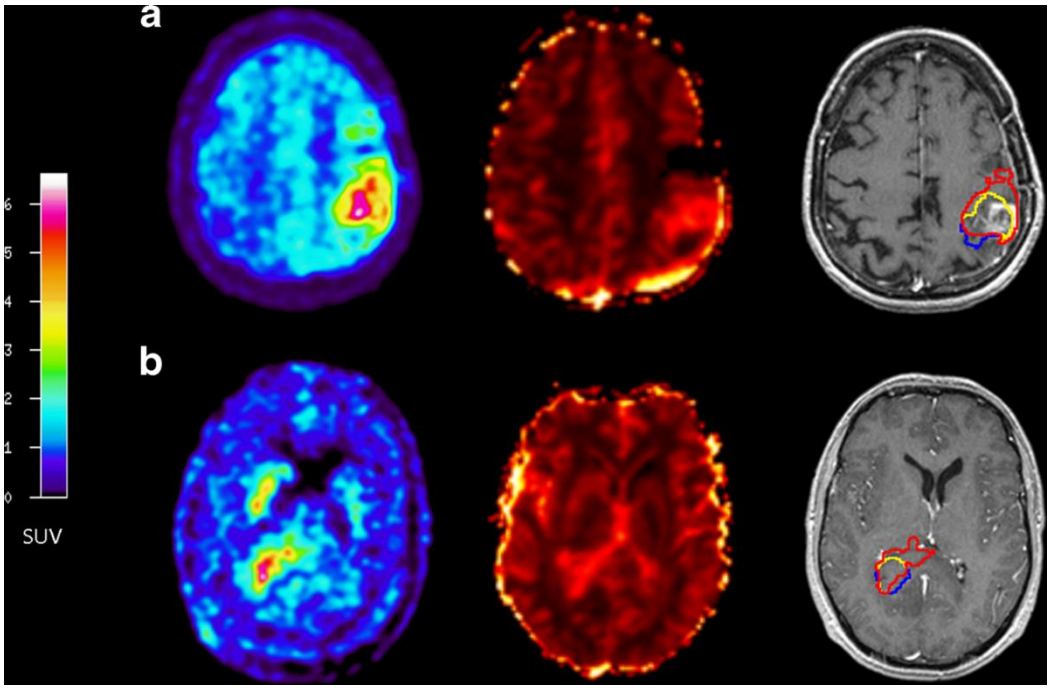

Figure 1. An example of spatial matching between tumor volumes from FDOPA-PET and rCBV images. These studies were selected from the studies with the highest volume overlap. From left to right: Contrast-enhanced T1-weighted image of axial FDOPA-PET, rCBV, and tumor VOI superposition (tumor volume from red FDOPA, tumor volume from blue rCBV, overlapping volume in yellow). **a** Patient 7, glioblastoma: FDOPA $_{vol\ 1.6}$ and rCBV $_{vol\ 1.6}$ are similar (25.55 ml and 26.30 ml, respectively). Spatial joint 31.8%. **b** Patient 34, uncontrast gliomatosis cerebo: FDOPA $_{vol\ 1.6}$ and rCBV $_{vol\ 1.6}$ are 19.12 ml and 7.17 ml, respectively; Spatial joint 12.49%.

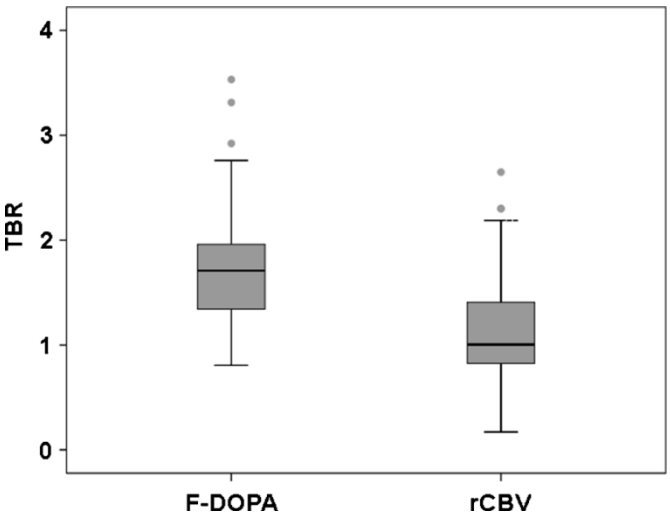

Figure 2. Boxplot of FDOPA uptake and tumor-to-brain ratio (TBR) of rCBV. The mean TBR for FDOPA uptake is significantly higher than the mean TBR for rCBV-TBR (1.76 vs. 1.14, p <0.0001, student's t-test on both sides).

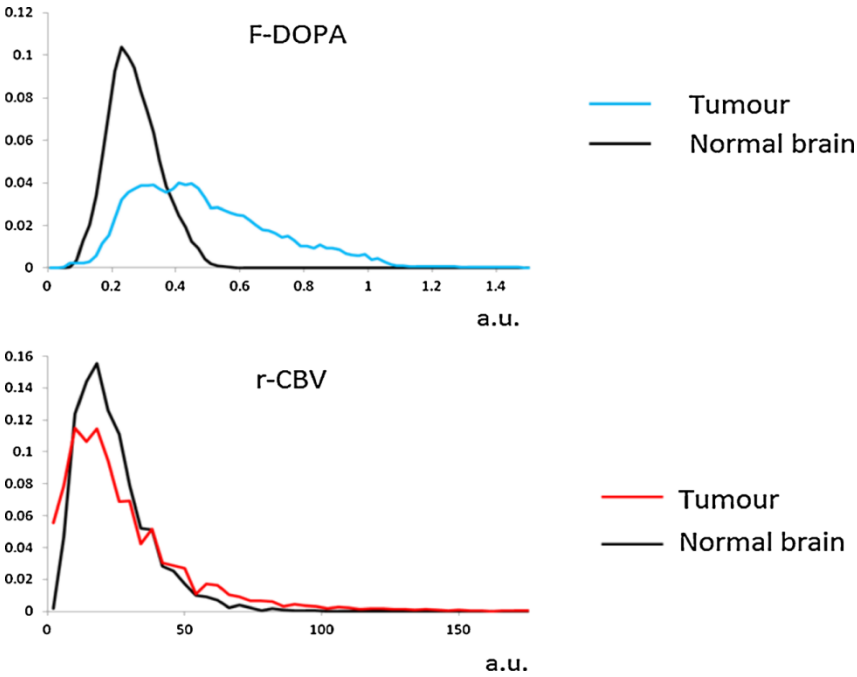

Figure 3. Mean histogram of FDOPA uptake signal and rCBV signal in tumor and normal brain. Incorporation of FDOPA allows tumors to be better isolated from the normal brain than rCBV.

	ce-T1-W volume (ml)[a]	F-DOPA$_{vol1.6}$ (ml)[a]	rCBV$_{vol1.6}$ (ml)	Total tumour volume (ml)[a]	O$_{vol}$ (ml)[a]	F-DOPA only (%)	rCBV only (%)	Spatial congruence (%)[a]
All studies (n=50)								
Median	1.18	11.44	1.04	12.26	0.28	89.95	5.61	1.38
Mean ± SD	3.24 ±4.9	22.59±34.9	3.13±4.8	24.20±35.2	1.51±2.9	78.10±27.1	16.67±26.5	5.21±8.4
High-grade(n=36)	2.53	18.69	1.61	18.75	0.49	89.95	5.61	1.60
Low-grade(n=14)	0.27	4.81	0.50	4.81	0	89.96	6.90	0

Table 1. Filss et al. Capacity analysis with mean and standard deviation of all studies to compare with the results of. Not all variables are normally distributed. [a]Variable in which the difference between high-grade glioma and low-grade glioma was statistically significant (Mann-Whitney U test)

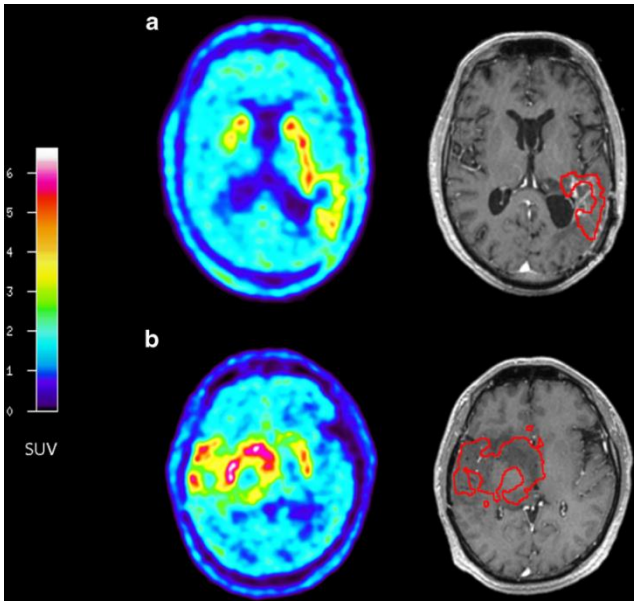

Figure 4. Interference pattern between physiological basal ganglia uptake and tumor boundaries. **a** Tumor uptake without striatal infiltration. The pathological signal does not overlap with the activity of the basal ganglia and a clear distinction is still possible. **b** Tumors infiltrate with large displacement of the basal ganglia, making it difficult to separate pathological and physiological signals. Tumor VOI is shown in both a and b.

7.Analysis

The first and most relevant result of our study in this chapter was to confirm that the TBR of FDOPA uptake was significantly higher than that of the rCBV chart (Figure 2), and that the FDOPA uptake of rCBV was significantly higher. Is a tumor as reflected in the histogram analysis, is a good normal brain (Figure 3). There was no significant difference in TBR between high-grade gliomas and low-grade gliomas. In summary, this study showed that FDOPA-PET and rCBV chart information differed significantly in patients with recurrent or progressive glioma. The image is easy to interpret and the FDOPA PET identifies larger tumor sizes than the rCBV chart. The integration of new diagnostic imaging methods may help assess the response to treatment and radiation therapy plans. However, the importance of the various tumor areas separated by these techniques should be investigated in prospective studies.

Chapter 4

The purpose of this chapter is to evaluate the therapeutic efficacy and diagnostic accuracy of ^{18}FDOPA-PET / CT in patients with glioblastoma or brain metastases, and then to release amino acid positrons for targeted depiction in radiotherapy schemes for high-grade gliomas. It was to evaluate the impact of dose measurement on tomography (PET).

1. Diagnostic accuracy of ^{18}FDOPA PET / CT in patients with glioblastoma or brain metastases

Glioblastomas and metastases are the most common malignant brain tumors. Brain metastases occur in 10-40% of systemic cancers, and non-small cell lung cancer is the primary tumor in about half of patients. In adult patients, primary brain tumors make up about 2% of all malignancies, and glioblastomas make up 15% of them. Magnetic resonance imaging (MRI) of the brain is the first imaging test to diagnose and monitor patients with brain tumors. Various sequences are typically performed, including T1-weighted image, contrast-enhanced polyplane, T2-weighted image, and fluid decay reversal recovery (FLAIR), diffusion, perfusion, and spectroscopy. However, the potential for brain MRI to visualize recurrent brain tumors and assess treatment-related changes (such as radiation necrosis and edema) is limited. In fact, the increased contrast on MRI is the result of increased permeability due to the disruption of the blood-brain barrier and may be due to radiation necrosis rather than being unique to tumor infiltration. MRI sensitivity is also suboptimal due to infiltration by high-grade gliomas outside the limits of contrast media. ^{18}F-3,4-dihydroxyphenylalanine (^{18}FDOPA) is a labeled amino acid analog used for positron emission tomography (PET) imaging. Increased uptake into brain tumors is associated with overexpression of the amino acid transporter LAT1 in tumor cells and their vascular system. This transport has nothing to do with changes in the blood-brain barrier. ^{18}FDOPA is recommended for imaging primary and metastatic brain lesions due to its high background ratio of tumor to normal brain. Previous studies have evaluated the effectiveness of ^{18}FDOPA PET

imaging for recently diagnosed or recurrent brain tumors through its technical and diagnostic outcomes. They demonstrated the excellent accuracy of ^{18}FDOPA

PET for imaging both low-grade and high-grade brain tumors. In addition, by Walter and others. ^{18}FDOPA PET showed that 41% of the range of primary and recurrent gliomas changed the intended treatment. The study was conducted using a brief interview with the referral doctor. Further research is needed to assess its effective ability to play a role in patient care and its complementary value to MRI. The purpose of this chapter was initially to positively assess the impact of the ^{18}FDOPA-PET study in the brain on treatment decisions for the Interdisciplinary Neuro-Oncology Tumor Board (MNTB) in patients with glioblastoma or brain metastases. Second, this study aims to quantify the improvement in diagnostic accuracy by adding ^{18}FDOPA PET to common MRI criteria.

2. Image acquisition, reconstruction, and interpretation

Two brain-centered imaging tests were performed: MRI and ^{18}FDOPA PET. The time lag between these two diagnostic imaging methods did not exceed the 28-day window.

1) MRI

MRI images were performed on a 1.5 T MR scanner with a head coil. The following sequences were performed: axial 3D T1 weighted GRE for anatomical overview, sagittal 3D T2 FLAIR FSE (CUBE) and axial T2 weighted FSE sequences for assessment of angiogenic edema and invasive tumors. Diffusion-weighted imaging (DWI) sequence (B = 1000) tumor cellularity evaluates spin-echo plane dynamic sensitivity contrast perfusion-weighted imaging (DSC PWI) as a surrogate manufacturer of angiogenesis and 3D T1-enhanced GRE contrast to assess gadolinium accumulation, evaluate the sequence (Dotarem®, 0.1 mmol / kg). Most MRI scans (93/106) performed spectroscopy to measure tumor metabolites. MRI was interpreted by a brain tumor radiologist using a complete sequence set and GE software.

2) ^{18}FDOPA PET / CT

Patients were rapidly administered protein for at least 4 hours. One hour prior to the injection of ^{18}FDOPA, 100 mg of carbidopa was orally ingested to reduce the activity of peripheral DOPA decarboxylase. Twenty minutes after infusion of 2 MBq / kg ^{18}FDOPA,

a special CT scan of the brain (120 kV, 80 mAs, 3 mm slice collimation) was performed, followed by a 10-minute static 3D PET acquisition of the center of the brain. The PET image is reconstructed using the iterative OSEM algorithm (5 iterations, 24 subsets) with scatter and attenuation corrected, but the point distribution function is not. For visual reading, ^{18}FDOPA-PET was systematically fused with contrast-enhanced T1-weighted MRI sequences. Image comparisons were performed using SyngoVia software using trilinear interpolation, rigorous comparisons, and mutual information algorithms. The images were qualitatively analyzed using a 4-point visual scale developed by Lizarraga et al. (Figure 1):

0: No pathological uptake (< contralateral occipital background)

1: contralateral occipital background < tumor uptake < contralateral striatal uptake

2: tumor uptake = contralateral striatal uptake

3: tumor uptake > contralateral striatal uptake

Scans with scores 0 and 1 are considered negative, scores 2 and 3 are recurrent or residual tumor infiltration. In our results, we can propose an algorithm for using ^{18}FDOPA-PET in brain tumors (Figure 3).

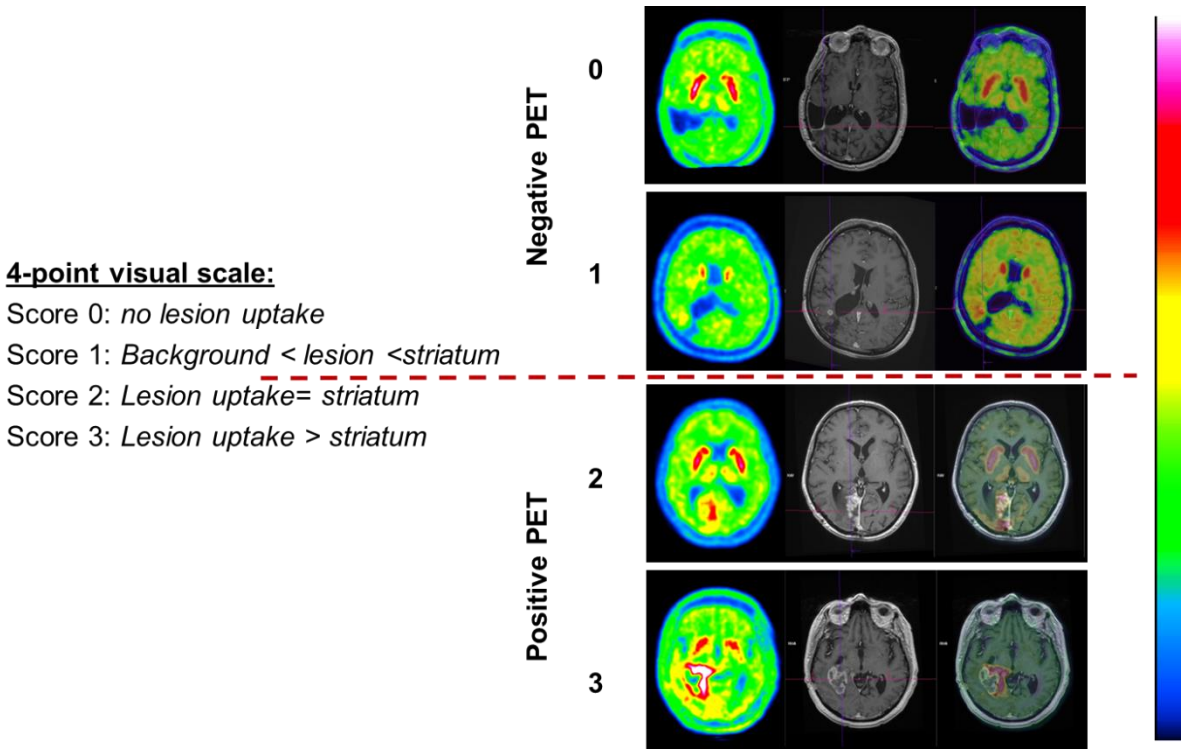

Figure 1. Visual interpretation of PET, ^{18}FDOPA PET image on the left. T1-enhanced MRI sequence with gadolinium contrast emphasized in the center. ^{18}FDOPA PET / MR image fusion right. The ^{18}FDOPA-PET

image was interpreted on a 4-point visual scale. The striatum image was used as an internal reference and the maximum color scale was set for the striatum.

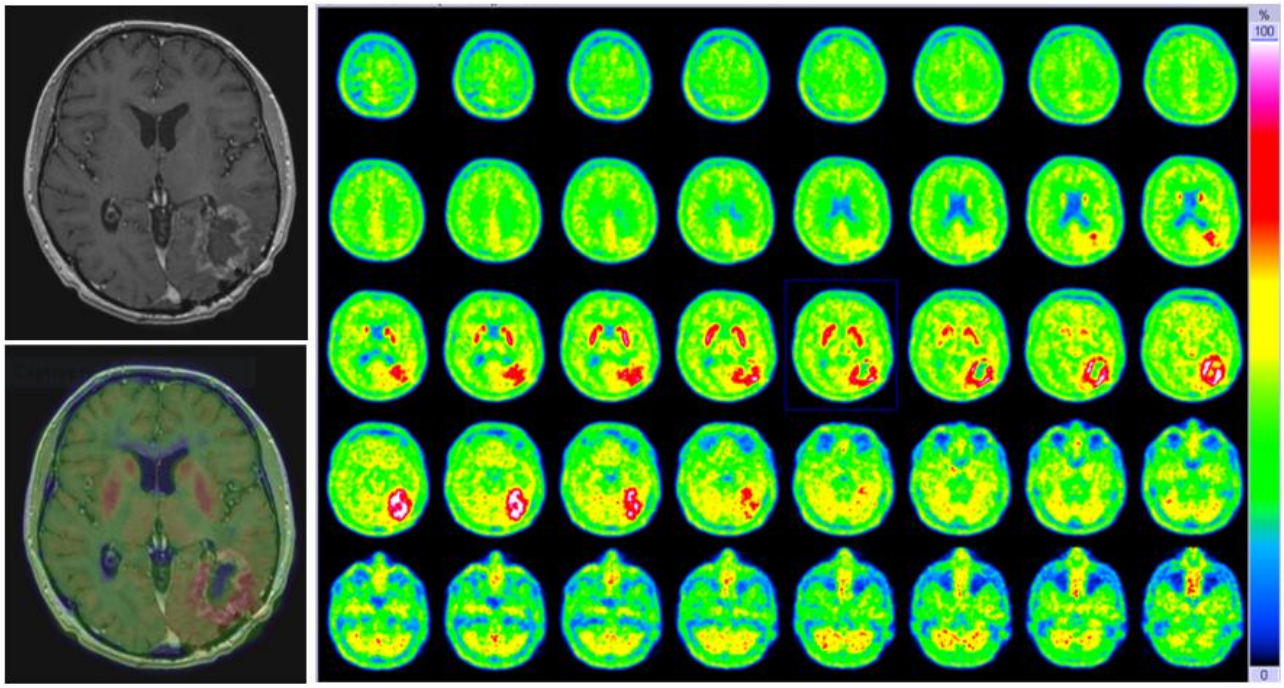

Figure 2. A case of a 60-year-old male patient with a history of left parietal lobe glioblastoma who benefited from complete surgical resections after chemoradiotherapy. Eleven months later, he suspected a clinical recurrence. However, based on medical history (MGMT methylation) and MRI data (morphological sequence, perfusion, spectroscopic analysis), the first MNTB suggested pseudo-progression as a diagnosis 1. And abstinence of treatment. The second MNTB was diagnostically suggestive of recurrence, as PET images showed high ^{18}F-FDOPA uptake around the necrotic lesion (level 3 score). 2 (change of diagnosis) and surgery (change of treatment). Pathology confirmed a central necrotic lesion surrounded by recurrent glioblastoma.

Upper left: T1 contrast-enhanced MRI. Right: ^{18}F-FDOPA PET image. Lower left: ^{18}F-FDOPA image fused with MRI.

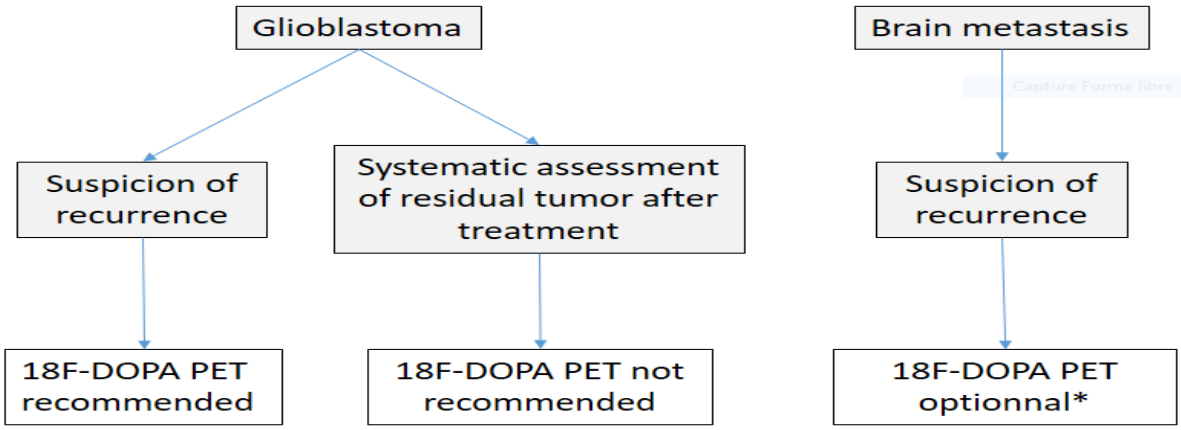

Figure 3. Recommended algorithm for using ^{18}FDOPA-PET in the treatment of brain tumors

* Only for suspicious positive MRI results based on the high negative predictive value of ^{18}FDOPA-PET.

3. Impact of dosimetry on amino acid positron emission tomography for target demarcation in radiotherapy planning for high-grade gliomas

3.1. Radiation Therapy Plan and Dose Assessment

Three patients with Grade III tumors had NCE gliomas. In these patients, limiting the volume of 60 Gy to areas with highly aggressive disease components, including PET biological imaging, aimed at a boost dose of 60 Gy, as determined by ^{18}FDOPA PET. A significant volume reduction occurred (Fig. 1). In patients with T1-CE, including ^{18}FDOPA PET may increase the volume by 60 Gy, as shown in Figure 2. Figure 3 shows an example of equal dose coverage in a treatment regimen where ^{18}FDOPA PET showed a high risk area within the T2 FLAIR signal anomaly. These structures were trimmed to stay within the brain parenchyma, reducing relative differences in PTV volume comparisons. As expected, this area was usually undertreated when the treatment plan for T1-CE patients was based solely on MRI imaging data, but was usually overtreated for NCE patients.

1.

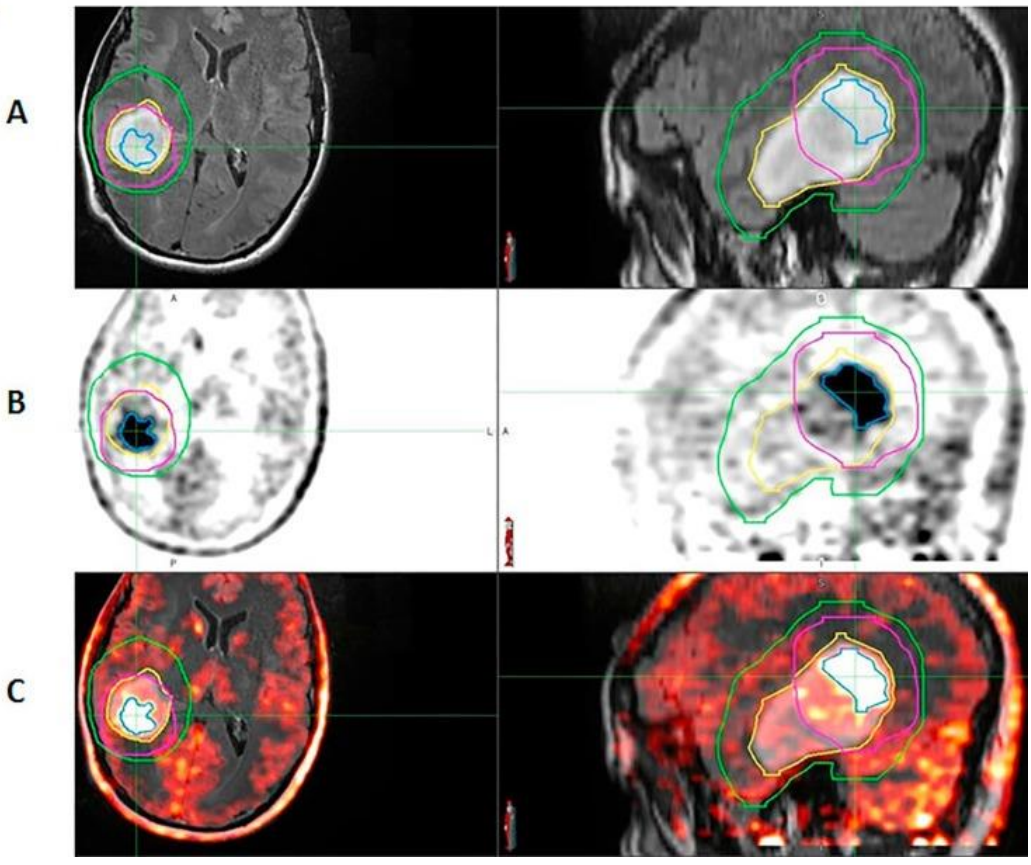

Figure 1. An example of the difference in 60 Gy target volume between MRI and MRI + PET in NCE patients. The upper row contains images of FLAIR MRI (A) and the corresponding ^{18}FDOPA PET (B) patient FDOPA 05, the middle row contains anaplastic astrocytoma NCE 2016 WHO Grade III, and the lower row contains MRI + PET fusion, explain that including PET in your plan can reduce 60 Gy of target area coverage. To illustrate the difference, I overlaid the PET-based contour on the MRI image. The reverse is also true. Legend: Blue = BTV_{60Gy}_PET; Yellow = GTV_{60Gy}_MRI; Magenta = PTV_{60Gy} (MRI + PET BTV_{60Gy} extension for PET planning); Green = PTV_{60Gy} MRI (GTV_{60Gy}_MRI extension for pure MRI planning).

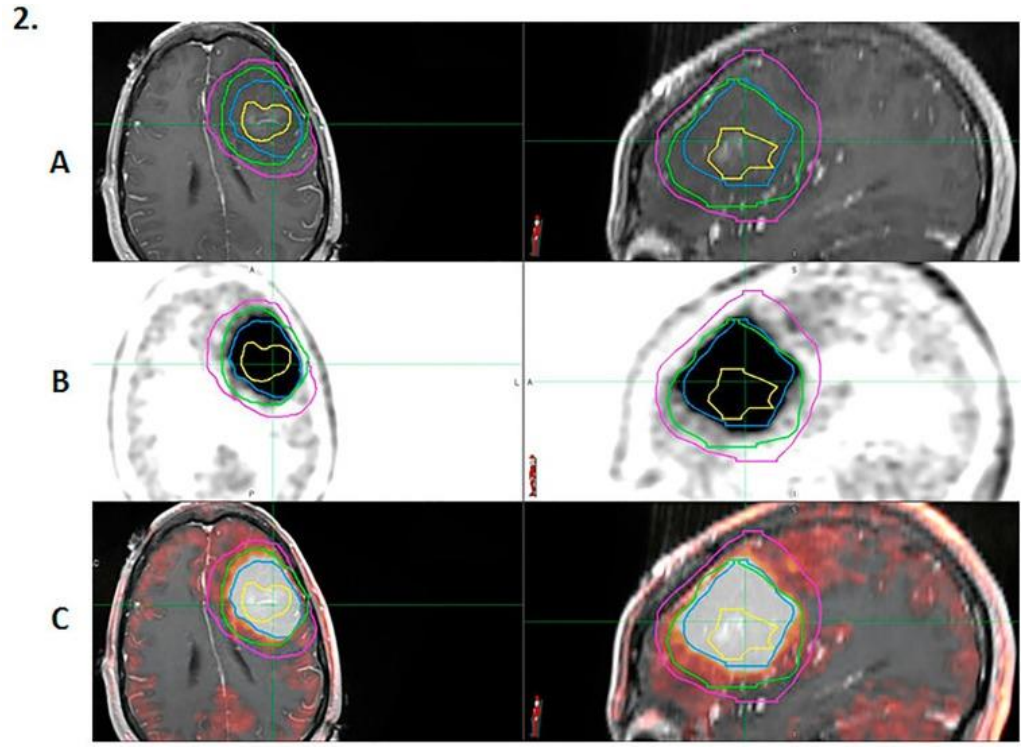

Figure 2. Example of difference in 60 Gy target volume between MRI and MRI + PET in T1-CE patients. The upper row is the T1-CE MRI (A), the middle row is the T1-CE 2016 WHO grade IV tumor (glioblastoma), and the corresponding ^{18}FDOPA PET (B) image of patient FDOPA 03, in lower row with MRI + PET fusion(C). A row showing an increase in 60 Gy target area coverage with PET scans above MRI T1-CE. Legend: Blue = BTV_{60Gy}_PET; Yellow = GTV_{60Gy}_MRI; Magenta = PTV_{60Gy} (MRI + BTV_{60Gy}_PET + GTV_{60Gy}_MRI extension for PET planning); Green = PTV_{60Gy} MRI (GTV_{60Gy}_MRI extension for pure MRI planning).

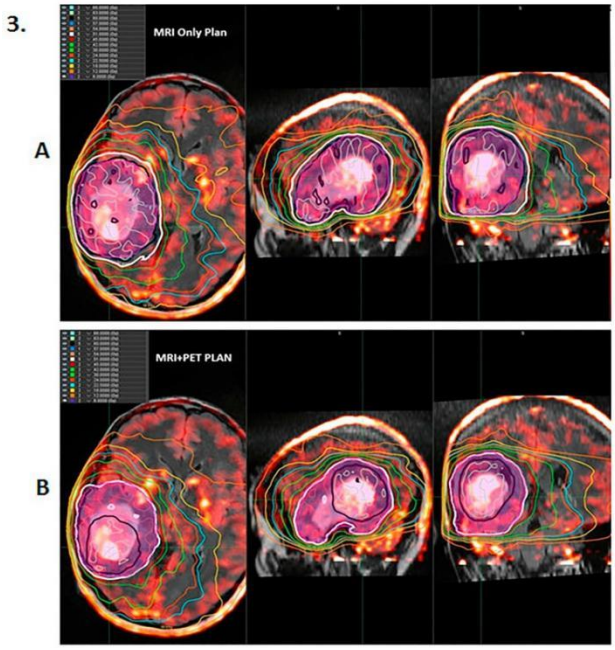

Figure 3. Isodose MRI (A) and MRI + PET (B) schemes. The black equal dose represents the prescribed dose (60 Gy). The magenta segment stands for PTV_{60Gy}. The discordant area was covered with 51 Gy (white equal dose) in the MRI + PET program (B).

In summary, our report shows that in NCE high-grade gliomas with integrated ^{18}FDOPA PET biological imaging, high-dose target volume was reduced and in T1-CE patients with ^{18}FDOPA PET biological imaging, it was shown that the volume of the area requiring high-dose radiation increased. Based on these results, a treatment plan based on ^{18}FDOPA PET appears to be feasible in patients with high-grade glioma. An appropriate dose range (V_{60Gy}> 95%) was feasible for PTV_{60Gy} PET + MRI volumes and all treatment plans met OAR limits.

Chapter 5

The purpose of this chapter is to determine the impact of carbidopa administration on the static, dynamic and radiometric parameters of ^{18}F-FDOPA PET imaging in brain tumors, followed by optimization of time to quantify absorption FDOPA collection in gliomas.

1.Effect of Carbidopa Pre-Medication on ^{18}F-FDOPA PET Imaging of Brain Tumors: Static, Dynamic, and Radiographic Analysis

L-3,4 dihydroxy-6-^{18}F Fluorophenylalanine (^{18}F-FDOPA) is a PET amino acid radiotracer that has been used to assess glioma for over 20 years. The PET RANO group (NeuroOncology response assessment) recommends that it be used for initial diagnosis, disease and treatment monitoring, and diagnosis of tumor recurrence. ^{18}F-FDOPA has a relatively high specificity for glioma and is given to the evaluation of glioma by its ability to cross the intact blood-brain barrier and overexpression of a large amino acid transporter (LAT) in tumors. Carbidopa (L-a-hydrazino-a-methyl b (3,4 dihydroxyphenyl) propionic acid) is a peripheral inhibitor of the aromatic amino acid decarboxylase. Therefore, its use as a premedication leads to increased plasma levels of ^{18}F-FDOPA and its metabolite ^{18}F-OMFD (3-O-methyl-6 [^{18}F] fluoro-L-DOPA). Carbidopa pretreatment increases radiotracer uptake in both healthy brains and gliomas, as ^{18}F-FDOPA K1 and the net inflow rate constant Ki are unaffected by this premedication. However, the rate of uptake into these two structures and the effect of premedication on carbidopa on radiomic parameters and dynamic analysis have not yet been determined. To date, only one study of two patients premedicated with 200 mg carbidopa has taken up the cerebellum, striatum, and tumor based on the acquisitions obtained 15-25 minutes after injection. It showed an average increase of 50%. In contrast to PET imaging of movement disorders, international guidelines do not recommend carbidopa before ^{18}F-FDOPA PET for brain tumor imaging. This is because most published studies do not use carbidopa.

2.Image analysis

Segmentation, using LIFEx software, defined tumor and contralateral healthy brain interest volume (VOI). Patient-specific crescent-shaped VOI, including both white and gray matter, was manually drawn into the unaffected hemisphere to measure healthy brain uptake as recommended. For tumors, VOI was semi-automatically segmented with a healthy brain SUVmean threshold of 1.6. Tumors with multiple loci were examined only at the time of neuropathological diagnosis. All final VOIs were visually

examined by an experienced physician (A.V.) to ensure that the quality of the methods used was consistent.

Parameter Extraction, For still images, the parameters SUVmean, SUVmax, and SUVpeak were extracted from the VOIs mentioned above for healthy brains and tumors. Radiomic analysis extracted 105 features from the same brain and tumor VOI. This included morphological, local intensity, intensity-based statistics, intensity histograms, and texture parameters. According to the guidelines and benchmark values of the Image Standard Biomarker Initiative, 103 parameters were extracted by PyRadiomics and 2 local intensity parameters that were not available by PyRadiomics were extracted by in-house software. These radiomix parameters were extracted as described elsewhere. Briefly, we performed isotropic voxel resampling using tricubic spline interpolation and then absolute discretization of PET intensity with a fixed bin size of 0.1. After all the 3D direction matrices were merged, the parameters were calculated from a single matrix. To potentially correct for any carbidopa premedication effects in our population, all static and radiomics parameters, except morphological features, in tumors were reextracted after normalizing each static image for the SUVmean of healthy brain VOI, to compute the Tumor to normal Brain Ratio (TBR) parameters. To take into account any potential patient movement during the dynamic acquisition, each dynamic frame was first registered to the associated CT image. The SUVmean values for each frame were respectively computed in the brain VOI and in the VOI corresponding to the tumor SUVpeak on the static image to extract the brain and tumor time activity curves (TACs). TACs were fitted to overcome noise effects. As previously defined, two dynamic parameters were extracted: time to peak (TTP) and slope. For parameters extracted from still images, a normalized version of the parameters was extracted from TAC to show the development of the relationship between the tumor and the brain-adapted TAC that may modify the premedication effect of carbidopa. Further analysis was performed on the simulation data to confirm the hypothesis (Supplementary Figure 1).

For statistical analysis, tumor VOI, linear regression analysis was performed to predict parameters using carbidopa status and tissue molecular diagnostics as covariates. This

is because tissue molecular diagnostics are known to affect static and dynamic parameters (gliomas are classified as IDH-wild type and IDH mutant astrocytoma, IDH mutation and 1p / 19q encoded oligodendroglioma, IDH wild-type and IDH mutant glioblastoma). The significance of each covariate was tested using a type III analysis of variance.

Effects of carbidopa, To confirm the hypothesis about the effects of carbidopa premedication on TTP and to better understand the effects on slopes, carbidopa premedication is based on the assumption that it caused an increase in radiotracers; performed a simulated TAC; Plasma concentration of ^{18}F-FDOPA without changing the input function, i.e. rate constant. Figure 2 shows an example of simulated premedication with carbidopa leading to increased TTP.

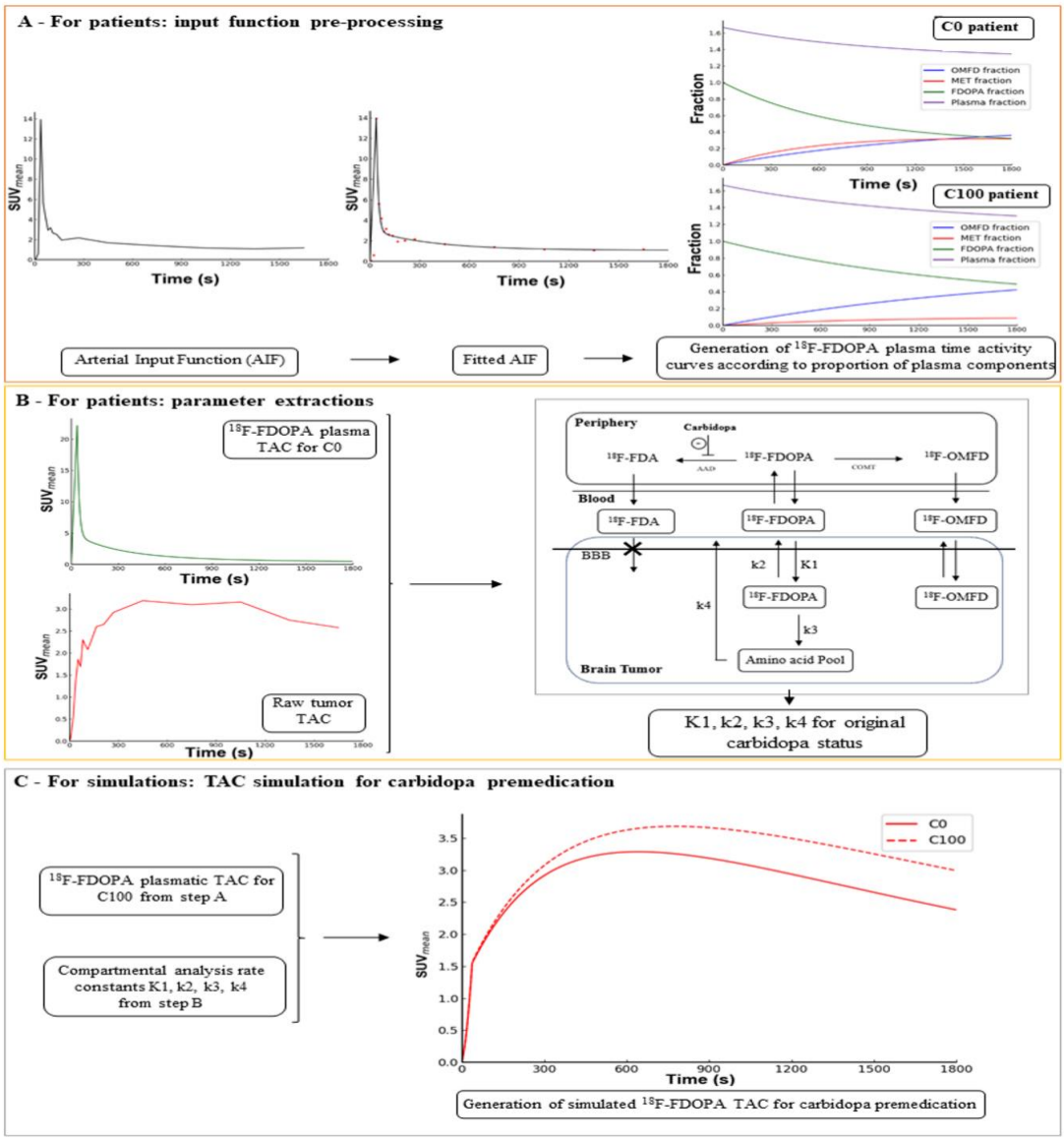

Figure 1. Supplementary data

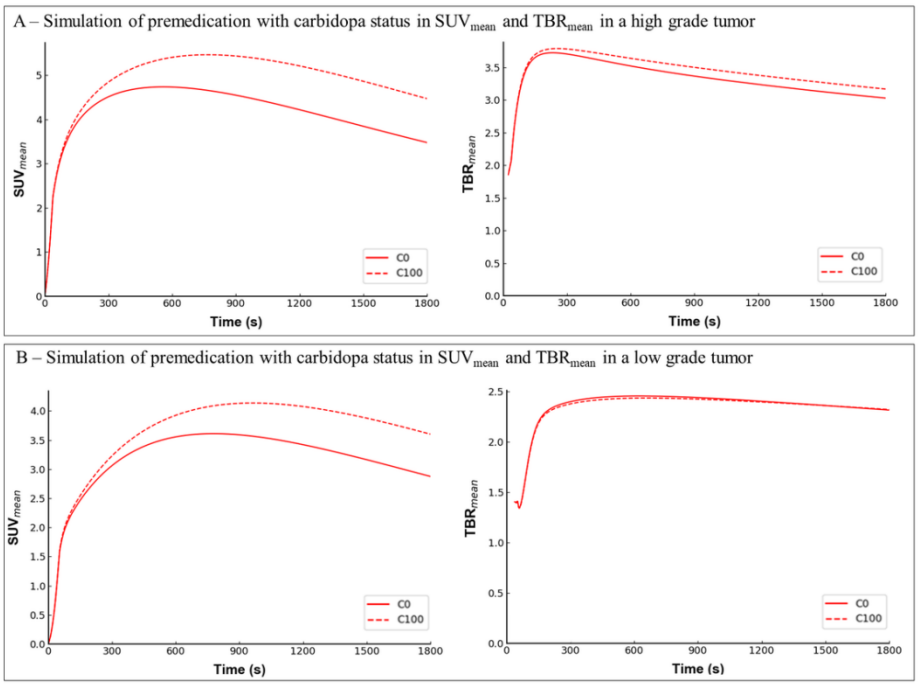

Figure 2. Typical examples of patients not taking carbidopa (C0) simulated the effects of 100 mg carbidopa (C100). A. PET ^{18}F-FDOPA time-activity curves are shown in SUVmean (left panel) of a 59-year-old woman with IDH wild-type glioblastoma. Carbidopa causes a longer TTP (TTP C0 = 9 minutes TTP C100 = 12.8mn) and an increase of the slope (slope C0 = - 4 SUV/h. SUV C100 = - 3.1 SUV/h). ^{18}F-FDOPA PET time activity curves expressed in TBRmean (right panel). The differences of TTP and slope values between carbidopa statuses are reduced when using Tumor to normal Brain ratio (TBR) images (TTP C0 = 3.8 mn vs TTP C100 = 4.2mn; slope C0 = -1.45 SUV/h vs slope C100 = -1.4 SUV/h). B. The PET ^{18}F-FDOPA time-activity curve is represented on the mean SUV (left panel) of a 65-year-old man with cervical tumour. Carbidopa produced a longer TTP (TTP C0 = 13.6 min. TTP C100 = 17.2 min) and increased slope (slope C0 = -0.7 SUV/h. SUV C100 = -0.3 SUV/h). ^{18}F-FDOPA PET time activity curves are represented by mean TBR (right panel). Differences in TTP values and gradients between carbidopa status were reduced using normal tumor-to-brain ratio (TBR) imaging (C0 TTP = 10.4 min vs C100 TTP = 11 min; degree slope C0 = -0.45 SUV/h versus slope C100 = -0.4 SUV/h)

3.Quantification of time frame binning to quantify FDOPA uptake in glioma

Quantification of 3,4-dihydroxy 6 [^{18}F] fluorophenylalanine-L (FDOPA) uptake in glioma assessment is time activity curve (TAC) It can be distorted by the next best time frame binning. Figure 3 shows an example of a typical TAC for a 50-year-old man. Undersampling or oversampling of dynamic PET images causes considerable variation in the quantification of kinetic parameters. Our goal was to optimize time frame binning

for dynamic FDOPA PET imaging. The FDOPA PET / CT imaging protocol consists of 10-20 minutes still image acquisition 10-30 minutes after injection. Semi-quantitative measurements of uptake values of tumor activity are calculated for routine clinical interpretation. However, the kinetic parameters obtained by dynamic acquisition may provide details about tumor characterization. For example, information about tumor aggression from FDOPA-PET / CT may guide biopsy and improve patient management through dose increases using intensity-modulated radiation therapy for glioma patients. Kinetic analysis requires time frame binning selected before reconstructing dynamic PET images. As far as we know, there are no recommendations for FDOPA PET / CT time frame binning for glioma dynamics analysis. To date, publications investigating the quantification of glioma uptake using complete kinetic analysis have used sampling in various time frames.

3.1.Selection of kinetics model

Pharmacokinetic modeling assumes that tracer kinetics can be divided into compartments by the flow of tracers from one compartment to another. The flow between compartments can be physical (transport through the membrane) or fictitious (between bound and unbound receptors or chemical transformations in the same physical space). In the current study, a reversible single tissue compartment model (1T2k + VB) (K1 = blood-to-tissue velocity constant, k2 = tissue compartment-to-arterial blood velocity constant, distribution (DV) = K1 / k2 and VB = Blood volume parameters), irreversible (2T3k + VB) and reversible (2T4k + VB) 2 tissue compartment models (tissue compartments represent the FDOPA pool of tumors, k3 = medial, k4 = lateral) were tested. These three compartment models are most commonly used for complete dynamic analysis of PET tracers in oncology.

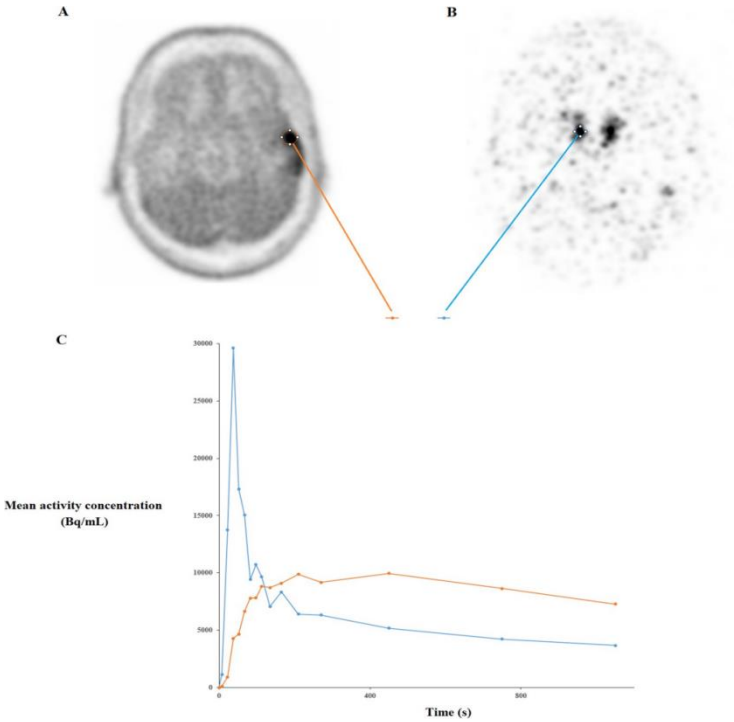

Figure 3. Axial PET FDOPA images show glioma resorption in a 50-year-old male (A) and FDOPA bolus (176 MBq) injected into the right middle cerebral artery (B) and arterial and glioma activity curves over time (C) give.

4.Analysis

This study from Chapter 5 showed that pre-preparation of carbidopa prior to ^{18}F-FDOPA PET imaging of brain tumors was associated with an increase in SUV, radiomic SUV and TTP dynamic parameters, which in general had about the same size as a healthy brain. For neurocancer PET indications, the efficacy of costly pretreatment with carbidopa is therefore limited by the use of TBR imaging and TAC ratios as effective tools for harmonizing studies multi-center. Pre-administration of carbidopa in the present study increased mean SUV levels by approximately 50% in healthy brain tissues as well as in brain tumors. This highlights the fact that the effect of carbidopa pre-administration is associated with a relatively uniform increase in the uptake of the radiosensitizer ^{18}F-FDOPA in VOI. The increase in SUVs associated with carbidopa use caused two simultaneous observations: 1) the shift of the texture matrix towards higher bin values (bin shift) mainly caused the modification of the parameters number correlated with SUV values and, 2) the relative disparity of the distribution of SUV values over a larger number of bins (barrel spread). The PET recommendations for ^{18}F-FDOPA for imaging parkinsonian syndrome recommend pre-treatment with carbidopa

to increase CNS and systemic availability of ^{18}F-FDOPA. This recommendation is quite different for brain tumors, since, unlike the striatum, brain tumor cells do not metabolise ^{18}F-FDOPA. This is probably why the ^{18}F-FDOPA PET scan recommendations do not include mandatory pretreatment of carbidopa prior to brain tumor scanning.

Chapter 6

This final chapter describes all materials and methods, including patient selection, ^{18}F-FDOPA PET image acquisition, parameter and image evaluation, statistical analysis, and results and considerations.

1. Materials and methods

1.1. Patient Selection

133 patients with primary brain tumors were included in this retrospective study (61 women and 72 men; mean age 46.1 ± 14.1 years). All patients underwent PET / CT examination with ^{18}F-FDOPA at Polyclinico Tor Vergata or Istituto Neurologico Mediterraneo Neuromed (Pozzilli, Italy) between December 2011 and March 2019. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Regional Ethics Committee of the University of Tor Vergata in Rome and Comitato Etico Istituto Neurologico Mediterraneo Neuromed. All participants or their legal guardians have given written consent. Subjects included in the retrospective analysis were selected according to adult age (18 years and older), diagnosis of primary brain tumors, and willingness to participate in the study.

Of the 133 patients: ◎

- 44 patients were affected by astrocytoma (33,1 %), of which one patient affected by Grade I pilocytic astrocytoma, Grade II 28 patients affected by astrocytoma, 15 patients affected by Grade III astrocytoma; ◎
- Three by Grade III anaplastic astrocytoma(2,2%) ◎

- Five by glioma(3,8) of which three patients affected by Grade II glioma, one patient affected by Grade III glioma, one patient affected by glioma(grade not identified/not reported); ◎
- 20 by oligodendroglioma (15%) of which 12 patients affected by Grade II oligodendroglioma, eight patients affected by Grade III Oligodendroglioma; ◎
- Four by Grade II oligoastrocytoma(3%) ◎
- Six by Grade IV glioblastoma(4,5%) ◎
- 1 by neurocytoma(0,8%); ◎
- And 50 not identified/not reported(37,6%)

1.2. ^{18}F-FDOPA PET Image Acquisition, Parameters, and Image assessment

According to other similar reports from our research group, PET/CT was performed in the ^{18}F-FDOPA group. For the reconstruction of PET images, we used ordered subset expectation maximization(OSEM) with four iterations and 20 subsets and a standard technique in a 3D model in a 256×256 matrix for the acquisition of the images. A low amperage CT scan of the head for attenuation correction (40 mA;120 kV) was performed prior to PET image acquisition. PET/CT images were acquired using a discovery VCT or a discovery ST 16 Scanner, 20 min. after the radiolabeled compound injection. All participants were injected intravenously with 4 MBq/kg(185±75 MBq) of ^{18}FDOPA and were hydrated with 500 ml of NaCl 0.9%. Carbidopa was not given prior to the radiopharmaceutical injection. Tumor site interest volume (VOI) was tracked by experienced nuclear medicine experts starting with the slice with the highest radiopharmaceutical uptake with the support of co-registered MRI images (hence, the correct placement of VOI involves the striatum). None of the patients in this study had a primary brain tumor in the occipital region. According to a previous study by our research group, the occipital region was selected for the background SUVmax calculation (SUVmax occ) obtained by placing a standard VOI of 1.5 cm x 1.5 cm x 1.5 cm in the occipital lobe. The SUVmax ratio is by Chiaravalloti et al. calculated as SUVmax lesions / SUVmax occ as described in a previous report. DTV is recorded as an FDOPA volume parameter (cubic centimeter) on a dedicated workstation (version 4.4, Advantage Workstation, GE Healthcare, Chicago, Illinois, USA), and TLDA is recorded

as an SUV average of and multiplied by the volume of interest calculated by DTV, according to Liu et al.'s nomenclature and approach.

1.3. Statistical Analysis

All variables were strongly biased and were converted before analysis. A linear regression model was created to evaluate the relationship between InDTV and InTLDA (dependent variables) with independent variables such as InSUVmax and InSUVmax ratios.

2. Results

In a univariate analysis, InSUVmax was positively correlated with InDTV (beta 0.42, p = 0.007) and the model described 6.2% of InDTV variance (Rsquare 0.62, StErr 1.13) (Figure 2). In addition, the InSUVmax ratio was positively correlated with InDTV (beta 0.80, p = 0.011) and the model described 23.8% of the InDTV variance (Rsquare 0.238, STED 1.13) (Figure 4). Similarly, InSUVmax was positively correlated with InTLDA (beta 1.27, p <0.0001) and the model described 50.2% of InDTV variance (Rsquare 0.502, STED 0.93) (Figure 3). The InSUVmax ratio was positively correlated with InTLDA (beta 1.87, p <0.0001) and the model described 24.6% of the InDTV variance (Rsquare 0.246, STED 1.14) (Figure 5).

2.1. Imagings

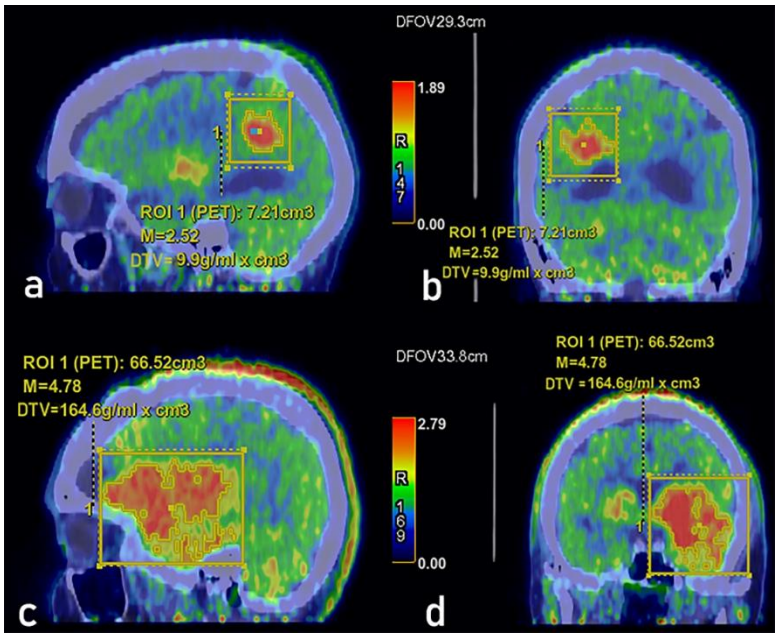

Figure 1. Total FDOPA activity of dopaminergic tumor volume (shown as DTV in the figure) and lesions on a dedicated workstation for calculation (version 4.4, Advantage Workstation, GE Healthcare, Chicago, Illinois) (shown as M in the figure); sagittal (a) and coronary (b) views of glioma II Patients, and glioblastoma IV in sagittal (c) and coronary (d) views of a patient. DTV and TLDA values correlate with SUVmax (see text).

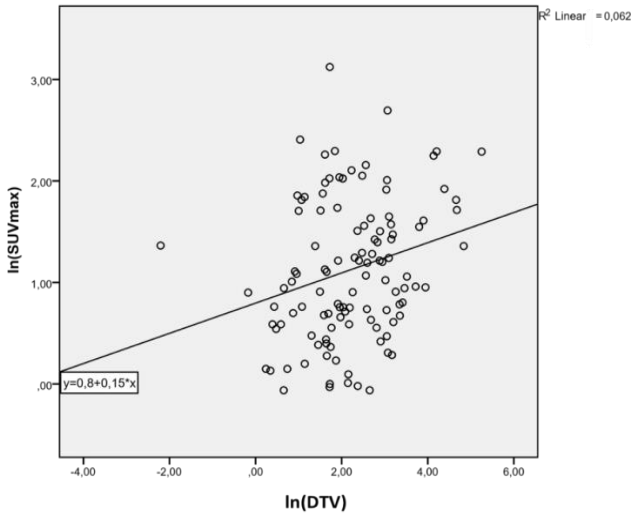

Figure 2. Relevant univariate analytical model between InSUVmax and InDTV

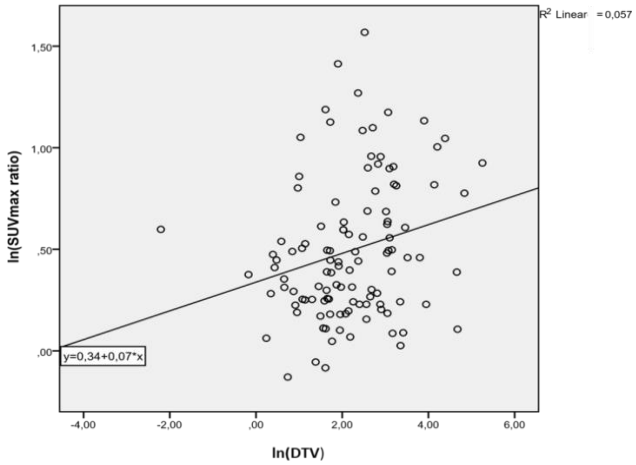

Figure 3. Univariate analysis model of the relationship between InSUVmax ratio and InDTV

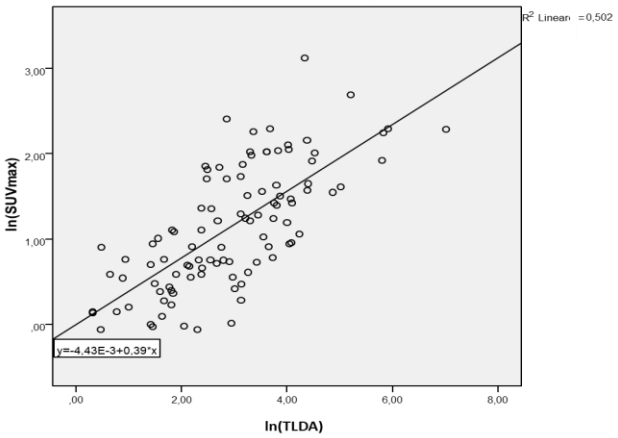

Figure 4. Univariate analysis model of the relationship between InSUVmax and InTLDA

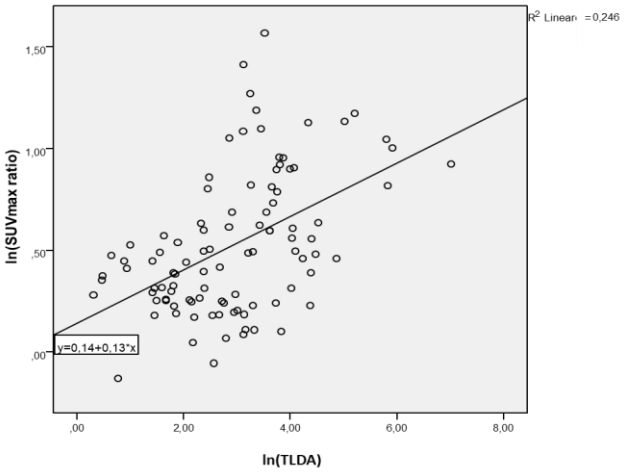

Figure 5. Univariate analysis model of the relationship between InSUVmax ratio and InTLDA

3. Discussion

Primary brain tumors are characterized by clinical heterogeneity with widespread tumor behavior. MRI is currently a reference imaging method for the diagnosis and follow-up of these tumors. The T1 and T2 emphasis sequences are sensitive to tumor size and location. However, because of some inconveniences with MRI, multimodal imaging, including functional imaging, is the most widely used approach. New PET tracers like amino acid tracers are very clear. For example, the role of PET / CT imaging in amino acid radiopharmaceuticals in the treatment of brain tumors is well established and widely used in clinical practice, including ^{18}F-FDOPA imaging. In ^{18}F-FDOPA imaging, in addition to visual interpretation, indicators derived from SUVs such as SUVmax and SUVmax ratio are routinely available information that can be used in

clinical practice to provide a better interpretation of PET / CT data, make it possible. The correlation between tumor characteristics and PET / CT indexes, especially the role of volume recording parameters such as DTV and TLDA, remains unclear. In fact, as far as we know, few studies have focused on the role of volume parameters in ^{18}F-FDOPA imaging, but there is more evidence for the volume uptake index in ^{18}F-FDG imaging. However, due to the promising role of volume index in ^{18}F-FDG imaging, we aim to focus on volume index in ^{18}F-FDOPA imaging as well. Therefore, in addition to the ratio of SUVmax to SUVmax, the parameter values for volume uptake were also discussed in this study. The purpose of our study is to improve knowledge of PET / CT indexes that may affect brain tumor management, especially the prognostic aspects of previously available evidence, of volume and SUV-derived parameters to evaluate the correlation. In previous reports, both DTV and TLDA in ^{18}FDOPA imaging were more strongly correlated with the risk group of pediatric neuroblastoma patients pretreated with both ^{18}F-FDOPA and ^{18}F-FDG. The authors evaluated the volume parameters of both methods and all indicators in comparisons between groups that differed by viability and clinical characteristics: Pretreatment ^{18}FDOPA and ^{18}F-FDG PET provided supplementary information, and volumetric indicators of ^{18}FDOPA and ^{18}F-FDG PET were more strongly correlated with risk group. These results confirm the potential role of the PET / CT volume index in ^{18}F-FDOPA, referring to a population that differs from our paper population in terms of age and histopathology. The role of PET/CT indices in the tumour management, particularly in the prognostic phase, generates interest and, therefore,we aim to correlate DTV and TLDA with ordinary SUV derived indices, to confirm the increasing importance of ^{18}F-FDOPA parameters in the tumor management, with potential implication particularly in prognostic aspects ^{18}F-FDOPA data interpretation and, subsequently, in the primary brain tumor management. Moreover, ^{18}F-FDOPA PET SUV derived indices are routinely available information easily accessed by using different dedicated workstations. Although patients with glioma recurrence/progression can be detected by static and dynamic ^{18}F-FDOPA PET parameters, most of this diagnostic information can be achieved by conventional static parameters, avoiding logistical disadvantages associated with the dynamic acquisition

as the increased acquisition time. According to our results, both SUV max and SUV max ratio positively correlate with DTV and TLDA. Therefore, our findings suggest that ^{18}F-FDOPA volume parameters, being correlated to uptake value as described by the correlation with SUV derived indices (both SUV max and SUV max ratio), are associated with an improved and ,more accessible evaluation in case of a higher uptake of radiopharmaceutical (in case of higher SUV). In a previous paper, a 2.5 SUV was used as a threshold for MTV and TLDA calculations. In another study, Metabolic Tumor Volume (MTV) was obtained by a 3D automated contouring process using thresholds corresponding to the SUV mean of the contralateral striatum. However, in order to correctly evaluate volume PET / CT parameters, various papers are needed to evaluate a particular minimum SUV threshold, and our results support this trend. We also want to focus on how to calculate the SUV max ratio based on previous studies by our research group, choosing the occipital region for background (SUV max occ) SUV max calculations rather than using ROI located in the centrum semiovale of the unaffected contralateral hemisphere, as described in other publications. However, the SUV quotient methodology and SUV quotient are uneven and still controversial. As far as we know, our study is the first to identify the SUV ratio based on the occipital background and compare the maximum SUV ratio (tumor to occipital) with the volumetric parameter: the maximum SUV ratio is positive on DTV ($P = 0.011$); the best correlation was the correlation between the maximum SUV ratio and TLDA ($p < 0.0001$). These results confirm the adequacy of our methodology for assessing maximum SUV ratios, while providing new insights into the volume ^{18}F-FDOPA index. Previous articles have linked maximal SUV ratios (scoring against contralateral uptake) to prognostic factors, emphasizing the importance of SUV-derived indicators for prognostic management, such as assessment and overall survival. In another study, the maximum SUV ratio was calculated taking into account striatal uptake (tumor striatal ratio) in low-grade gliomas. However, according to previous publications, all SUV-derived indicators studied (including SUV max) can accurately distinguish between low-grade gliomas and high-grade gliomas and correlate most closely the indicators were SUV mean tumor / normal brain ratio (T / N) and SUV mean tumor / striatal ratio (T / S).

Therefore, in this study, the ratio of tumor uptake to normal tissue uptake by dividing the tumor SUV by the contralateral centrum semiovale (T / N) SUV and the striatal SUV (T / S) has been generated. However, the maximum SUV ratio calculated with occipital uptake was also associated with good prognostic performance, which correlates with both progression-free survival (PFS) and overall survival (OS). In contrast, the results of ^{18}F-FDOPA PET / MRI imaging to monitor response to treatment in another study reported that maximal and mean SUV to tumor-to-brain ratios were not predictors of response. On the other hand, in the same article, the authors described a trend in the percentage of DTV change observed in the 4-week examination, which correlates with progression-free survival. In another work that determines the prognostic value of volumetric parameters derived from the pretreatment of ^{18}F-FDG and ^{18}F-DOPA PET/CT of neuroblastoma and their correlation with clinical and histopathological characteristics, only volumetric indices (DTV, TLDA, MTV and TLG) differed significantly among risk groups. It seems clear that the emerging role of volumetric uptake parameters is gaining interest in the scientific literature with heterogeneous results, so more studies are needed focused on the correlation with other variables, including other PET parameters. However, our results confirm the increasingly important role of the SUV max ratio in image interpretation. More multicenter studies on larger samples are needed to eventually arrive at a proper classification of patients with primary brain cancer based on PET/CT indices, but to date we can consider PET/CT indices as valuable tools that can help in image analysis. However, our results confirm the importance of calculating the SUV derived indices and the volumetric acquisition parameters in the PET/CT evaluation. Surprisingly, the best correlation between SUV max and SUV max ratio and TLDA is described. These results support the interest in ^{18}F-FDOPA volumetric indices.

Conclusion

In characterization of both primary high-grade and low-grade brain tumors, ^{18}FDOPA appears to be a suitable tracer, especially in the diagnosis of low-grade brain tumors that cannot be significantly enhanced by contrast-enhanced MRI. In particular, this tracer can be used for semi-quantitative measurements of SUVmax by characterizing the grade of the tumor. With regard to brain metastases, its role appears promising, especially in patients with functioning neuroendocrine tumors due to their high T / N ratio. The results of our study indicate that [^{18}F] FDOPA PET / CT may play a role in identifying primary brain tumors and predicting OS and PFS in patients with low-grade but non-high-grade primary brain tumors. Our study shows that the ^{18}FDOPA PET / CT volume uptake parameters are easier to assess in primary brain tumors with a high SUVmax to SUVmax ratio. Our results also confirm the important role of maximal SUV ratios calculated using tumor occipital ratio in image analysis of primary brain tumors with ^{18}FDOPA PET / CT. Although more work is required, our results confirm the potential role of volumetric parameters in ^{18}F-FDOPA imaging as well. In summary, ^{18}FDOPA is an important and promising tracer and may mark a particular area of molecular imaging of brain tumors using PET / CT in the coming years. However, future research is needed to truly assess its clinical utility in this particular area. Since the last EANM guideline in 2006, the clinical application of PET and PET / CT molecular imaging in the diagnosis of glioma has continued to increase in Europe and the United States. Proper use of this technology requires a clear understanding of the technology's features and limitations, as well as proper patient selection, preparation, scan acquisition, and image reconstruction. Our current study documents the effect of carbidopa premedication on ^{18}F-FDOPA PET imaging of brain tumors. Premedication with carbidopa leads to increased availability of ^{18}F-FDOPA in plasma without altering the rate constant. Carbidopa pre-medication increases SUV, SUV-dependent radiomics, and TTP dynamic parameters in healthy brains by the same number of digits as tumors, so these effects are considered in still images or tumor-to-health effects. That will be

shown after the brain ratio is corrected by the time activity curve. This is an important point for the harmony of multicenter joint research.

Annex

I. Optimization of quantification of kinetic FDOPA absorption samples

Undersampling or oversampling can cause significant variability in quantification of kinetics parameters. To optimize the quantification of dynamic FDOPA uptake, the purpose of this study was to define optimal temporal sampling of the FDOPA-PET / CT reconstruction protocol in patients with glioma. First, our results showed TBRmax at 20 minutes p.i. was significantly higher than 35 minutes p.i. In addition, TBRmax at 20 minutes p.i. always higher than 35 minutes p.i in all tumors. Several studies have previously examined changes in glioma FDOPA uptake over time. By Chen et al. the best tumor FDOPA uptake was shown to occur between 10 and 30 minutes after injection. Similarly, from Schiepers et al. published studies show that the maximum activity of tumor FDOPA uptake is about 20 minutes p.i. achieved. In two recent studies, TAC for tumor FDOPA uptake reached p.i. in 8-10 minutes early. However, the EANM / EANO / RANO practice guidelines / SNMMI procedural criteria for imaging gliomas using PET have recently recommended 10-20 minutes of imaging with a 10-30 minutes p.i. is done.

Second, using full quantification, two studies compared FDOPA influx with tumor grade. On the one hand, Schiepers et al. has suggested that newly diagnosed high-grade brain tumors had a significantly higher K1 score than those extracted from low-grade brain tumors. Meanwhile, by Kratochwil et al. there was no significant difference in K1 levels between high-grade and low-grade brain tumors. Possible explanations for these inconsistent consequences may be linked to the dynamic time sampling protocol. The protocol was different in the latter two studies.

Third, the reversible single tissue compartment with Akaike's criterion, blood volume fraction was the preferred dynamic model to explain FDOPA uptake in gliomas. To our knowledge, only two studies evaluated compartment modeling to quantify FDOPA uptake in gliomas based on dynamic PET scans. Schiepers et al. showed that the error estimates for the two-histological compartment model were significantly smaller than those for the one-histological compartment model. In fact, by Kratochwil et al. it was

suggested that K1 predominates in FDOPA uptake for the first few minutes after injection. By Nioche et al. the findings confirm this result and show that FDOPA uptake of gliomas extracted in a two-tissue compartment model is very similar to uptake in a single-tissue compartment model over a 45-minute PET study period.

Fourth, this study showed a strong correlation between SUVmax and uptake rate constants, as determined by either Logan's graph analysis or pharmacokinetic modeling. Simple static measurements are sufficient instead of dynamic PET scans to quantify FDOPA uptake in gliomas. However, more research is needed to confirm these results. This study has some limitations. First, although the sample size was relatively large, the number of patients was limited. Second, the input function used for PET dynamic modeling was not obtained from arterial sampling. However, the FDOPA plasma input function was obtained after correcting metabolite and hematocrit values based on data from previous publications. In recent studies, the plasma input imaging feature has also been used to quantify FDOPA glioma uptake. Third, fluctuations in methodological factors such as FDOPA dose, non-TOF PET systems, image reconstruction, post-filtering, and dynamic tracer modeling can bias K1 estimates. Time sampling of 8x15 seconds – 2x30 seconds – 2x60 seconds – 3x300 seconds has proven to be optimal with the parameters of modern PET systems.

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