Current status of ^{18}F-DOPA PET imaging in the detection of brain tumor recurrence

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Abstract
Considering the intrinsic limits of fluorine-18-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) for diagnosing brain tumors and tumor recurrence, several radiopharmaceuticals have been developed to detect brain tumor recurrence after treatment. Among others, a promising tracer is fluorine-18-desoxyphenylalanine (DOPA), due to its very low rate of physiological distribution in normal brain structures of white and grey matter. The aim of our study was to assess the feasibility of PET/CT with ^{18}F-DOPA in the detection of brain tumor recurrence after treatment, in comparison with MRI performance and other PET radiopharmaceuticals, currently employed in this field. **Conclusion**: The ^{18}F-DOPA PET/CT seems to be useful in the diagnosis of patients with suspected brain tumor recurrence, because of low signal ratio in normal brain white and grey matter, in particular as compared to ^{18}F-FDG PET/CT low performance. Related data are presented for other fluorinated amino acid tracers. Magnetic resonance imaging is the gold standard of diagnosis and ^{18}F-DOPA PET/CT is adjuvant to diagnosis. Further studies are needed to enrich our knowledge about this promising tracer,^{18}F-DOPA, especially on its possible role onsemi-quantitative measurements in brain tumors.

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Introduction

Today, the most useful positron emission tomography (PET) tracer for the evaluation of tumors and monitoring response to treatment in various malignancies is fluorine-18-fluoro-2-deoxy-D-glucose (^{18}F-FDG), a radiopharmaceutical representative of glucose metabolism in cancer cells. The uptake of ^{18}F-FDG in neoplastic tissues is a consequence of the increased expression and activity of glucose transporter proteins and of glucose phosphorylating enzyme, hexokinase [1]. Fluorine-18-FDG PET is usually combinedwith computed tomography (CT). Nevertheless, there are several limitations, due to the intrinsic properties of the tracer as an analogue of glucose such as its use in tumors with low grade of glucose metabolism and also the possibility of uptake of the tracer by benign lesions like inflammation [2] and the high rate of distribution of this tracer in the brain [3].

Brain tumors can be divided into tumors of neuroepithelial tissue: astrocytomas, oligodendromas, oligoastrocytomas, neuronal and mixed neuronal/glial tumors. These tumors, even with a different grade of malignancy, are characterized by a tendency to recur despite their surgical and/or radiotherapy treatment. In this review we do not focus on other brain tumors, such as tumors of the pineal region or on embryonal brain tumors, since these tumors have a different etiology, treatment procedure and prognosis.

Some other radiopharmaceuticals are currently employed or under study in molecular imaging with PET/CT, such as ^{11}C-methionine (^{11}C-MET) [1], ^{18}F-fluorothymidine (^{18}F-FLT) [4], ^{18}F-fluoroethyltirosine (^{18}F-FET) [5] (^{18}F or 11C) choline [6], ^{18}F-fluoromisonidazole (^{18}F-MISO) [7] and ^{18}F-fluoro-3,4-dihydroxy-l-phenylalanine (^{18}F-DOPA) [8]. Even if characterized by different metabolic pathways, all these tracers have a very low rate of distribution in brain structures that allows the recognition of functional disorders or of brain tumors and metastases.

The^{11}C-MET has a high degree of uptake in neoplastic tissue due to its role as an essential amino acid form, necessary for protein synthesis. Unfortunately, the short half-life of 11C (20min) [9] limits its availability. So, several fluorinated amino acid tracers (^{18}F-FET, ^{18}F-FLT and ^{18}F-DOPA) are currently under study [10]. These traces have a longer half-life that makes them clinically, available in many diagnostic centers.

On the other hand, only few studies have studied the role of ^{18}F-choline PET/CT in the diagnosis of brain tumors or tumors recurrence [11, 12].

The ^{18}F-DOPA is an amino acid analog used as a PET tracer labeled with ^{18}F and can be widely clinically applied because of its longer half-life. Since the biological component of DOPA is the precursor of dopamine, this tracer was firstly employed in the management of patients with movement disorders, in particular Parkinson's disease [10, 13, 14]. Its potential role in the diagnosis of some psychotic diseases is still investigated [15, 16]. Injected ^{18}F-DOPA is normally detected in the brain in substantia nigra and in the caudatum and putamen nuclei, which are similar in structure and have a common embryologic origin [17]. Therefore, ^{18}F-DOPA has been proposed for the diagnosis of primary brain lesions, especially because of its high uptake in tumors in oppose to its very low uptake in normal brain tissues, other than basal ganglia [8]. This feature should allow, detection of tumors relapse after surgery and/or radiotherapy [18].

Other studies have described the feasibility of ^{18}F-DOPA in the management of newly diagnosed brain tumors [4, 19-21]. The attention of this review was centered in studying whether ^{18}F-DOPA PET/CT can be effectively used in the diagnosis of recurrent brain tumors as is the case in brain gliomas [22].

^{18}F-DOPA PET/CT in recurrent brain tumors

All researchers agree about the usefulness of an early PET acquisition, few minutes after tracer administration, considering the rapid peak of tracer uptake in tumor cells. In particular, Becherer et al. (2003) [1] demonstrated that, although the basal ganglia showed faint uptake of ^{18}F-DOPA at 20min after injection, tumor visualization was not hampered at that time, while in the late scans at 70min post injection, tumor uptake appeared less pronounced while there was markedly increased uptake in the basal ganglia. Other authors suggested that an early acquisition, 20min after tracer administration, was the best time to perform the test in patients with gliomas [21] while others suggested 10 or 20min [8, 20]. Nevertheless, it was interesting to notice that even a late acquisition at 70-90min was associated with good visualization of the basal ganglia [1].

Regarding the detection rate of brain tumors relapse, in patients with suspected recurrent gliomas or brain metastases, Chen et al. (2006) [20], using ^{18}F-DOPA and ^{18}F-FDG PET/CT in 23 brain tumor patients previously treated by radiotherapy with or without surgical resection, found false-negative results by ^{18}F-FDG PET/CT while ^{18}F-DOPA correctly differentiated recurrent low grade tumors from necrotic tissues. All patients without active tumors showed no visible ^{18}F-DOPA uptake. The authors concluded that ^{18}F-DOPA was superior to ^{18}F-FDG in evaluating recurrent low grade gliomas, also difficult to evaluate with MRI. Furthermore, they showed lower standardized uptake values (SUV) [23] in glioma patients than did ^{18}F-FDG PET and higher contrast between tumor tissue and normal tissue. The encouraging results of this study were limited by the low number, of only 30 patients examined by both tracers.

Becherer et al. (2003) [1] examined 20 patients with various types and stages of gliomas and astrocytomas including metastatic disease. Among these, 15 had residual or relapsing tumors after surgery and/or radiotherapy or chemotherapy. They compared the detection rate of ^{18}F-DOPA PET with that of ^{11}C-MET in all patients and found that these two tracers showed a matching image pattern upon visual assessment, regarding tumor size and shape, with a sensitivity of 100% for both patients' basis and also per lesions analysis. Furthermore, the SUV of ^{18}F-DOPA and ^{11}C-MET at 20min showed a significant correlation ($P<0.05$). The authors concluded that, since the diagnostic performances of the two tracers were similar (probably due to their common metabolic pathway) and the use of ^{11}C-MET in PET centers without a cyclotron was impossible, ^{18}F-DOPA should be considered as an analogue to ^{11}C-MET for the diagnosis of primary brain tumor's and of tumors' recurrence. Unfortunately, only 5 patients after PET scan had additional histology, to ensure the diagnosis. Other limitations of the above study were the heterogeneity of examined patients, the fact that the patients were previously submitted to different therapies, were in different health statuses, and had different grades of tumors like: glioblastoma grade IV, astrocytoma grades I, II, II and IV and oligodendroglioma grade II [1].

Another study compared the diagnostic accuracy of ^{18}F-DOPA PET/CT with that of ^{18}F-FLT and of ^{18}F-FDG, in previously treated recurrent low grade gliomas (grades I and II) and in patients with remission [4]. In this population, ^{18}F-DOPA PET/CT was positive in all cases and negative in all patients in remission while ^{18}F-FDG and ^{18}F-FLT PET/CT showed insufficient results. Moreover, ^{18}F-DOPA and ^{18}F-FLT, similarly to previous studies with amino acid tracers [1, 9, 20] showed a better ratio of tumor uptake to normal brain tissue uptake (T/N) than ^{18}F-FDG, because of the lower distribution of amino-acid analogues tracers in normal brain, as mentioned before [4].

The potential differences between ^{18}F-DOPA PET/CT and ^{18}F-FET PET/CT were recently examined by Kratochwil et al (2014) [24] in 16 patients, 8 with recurrent low-grade astrocytomas and 8 with high-grade glioblastomas. The authors demonstrated superior contrast ratios for lesions outside the striatum examined by ^{18}F-DOPA, although semi-quantitative measurement of SUV did not correlate with tumor grading. Furthermore, they observed that ^{18}F-FET could provide additional information on tumor grading but showed lower striatal uptake, lower contrast ratios and used a longer time for late images.

The diagnostic accuracy of ^{18}F-DOPA PET/CT and ^{18}F-FET PET/CT was also compared in a paper by Lapa et al. (2014) [25]. Their conclusion, in a population of only high grade gliomas (22 recurrent and 5 primary), was that ^{18}F-FET PET/CT, by visual analysis, revealed no significant differences in uptake pattern, while semi-quantitatively the SUV was significantly higher for ^{18}F-FET than for ^{18}F-DOPA, suggesting a better performance. Regarding tumor delineation, both tracers performed equally well and seemed equally feasible for imaging of recurrent high grade gliomas. Nevertheless, the examined population was poor to give a meaningful statistical analysis and patients were examined with different tumor grades and health status.

In 91 patients studied by ^{18}F-DOPA PET/CT and MRI, Ledezma et al. (2009) [19] reported that in 11 patients with

recurrent tumors, ^{18}F-DOPA PET/CT was positive in all cases (sensitivity 100%), while the diagnostic accuracy of MRI was substantially improved by PET/CT in detecting brain tumor relapse. Therefore, ^{18}F-DOPA PET/CT could improve the diagnosis of residual tumors, not clearly detectable on MRI. In particular, ^{18}F-DOPA activity was sometimes seen in regions of subsequent tumor recurrence, during the follow-up, when MRI was negative.

Various papers have demonstrated that glioma cells are commonly found beyond the area of contrast enhancement in MRI, especially in tumors with high grade. The enhancement of contrast media in MRI depends on blood-brain barrier permeability that can be affected during necrosis induced by chemotherapy or radiotherapy. Moreover, necrosis by itself can show meaningful contrast enhancement [19]. Even in the cited study the examined patients were only 21.

The above findings were recently confirmed by an interesting paper [26] who examined a population of 35 patients with clinical suspicion of recurrent gliomas in a prospective study. Among these, 26 patients were positive and 9 negative for recurrence. The sensitivity, specificity and accuracy of MRI were 92.3%, 44.4% and 80% respectively whereas those of ^{18}F-DOPA PET/CT were 100%, 88.89% and 97.1% respectively. Furthermore, MRI and ^{18}F-DOPA PET/CT were concordant in 29/35 and discordant in 6/35 of patients. Finally, the ^{18}F-DOPA PET/CT was more specific than MRI for both high-grade and low-grade tumors. The most important feature of this paper was the best inclusion-criteria that allowed a more homogeneous population and a better recognition of the diagnostic accuracy of ^{18}F-DOPA PET/CT versus MRI, although the number of examined patients was limited.

Other researchers also investigated the possibility to use a dynamic acquisition for diagnosis that could help to better define the progressive uptake of the lesions by means of the SUV [27]. In 10 patients with recurrent low and high grade brain tumors they confirmed that static and dynamic imaging could detect relapse of low and high grade brain tumors, with the help of both visual and semi-quantitative analysis. These findings were confirmed by Herrmann et al (2014) [28], who examined with ^{18}F-DOPA PET/CT glioblastoma patients visually, with a 5-point scale and semi-quantitatively by lesion-to striatum and lesion-to normal brain tissue ratios using both SUV mean and SUVmax. Furthermore, the accuracies for recurrence detection studied using histopathology and clinical follow-up glioblastoma were similar for visual (82%) and semi-quantitative (range, 77%-82%) analysis. Both analyses were significant predictors of progression-free survival. Therefore, both visual and semi-quantitative indices detected glioblastoma recurrence with high accuracy and were predictive for progression-free survival. This last feature considering the large number of patients studied (110 patients) and the homogeneity between patients, which stands also to their's clinical and anamnestic data seems to be an important finding.

Considerations and perspectives

Besides neuroendocrine tumors and pheochromocytomas [29, 30], the ^{18}F-DOPA has been used for the study of primary and recurrent malignant brain tumors. Malignant cells proliferations are linked to increased use of amino acids for protein synthesis and mitosis, also associated with an over expression of aminoacids transporter system. For this reason, ^{18}F-DOPA PET/CT shows an overall better accuracy in detecting brain tumor relapse versus ^{18}F-FDG. Additionally, the diffuse uptake of ^{18}F-FDG in the normal structures of both the white and grey matter makes the recognition of malignant processes difficult [31]. Furthermore, in case of inflammation, ^{18}F-FDG may give false positive results [32]. Cancer cells can also show different uptake patterns, classified as with low, mild or higher uptake and all these uptakes could be difficult to identify from normal brain structures.

Due to its very low rate of bio-distribution in the brain, ^{18}F-DOPA seems to be very useful in detecting tumor relapse after surgery or radiotherapy, and in indicating residual tumors, with a better accuracy than ^{18}F-FDG [20].

In respect to the other main tracer employed in this field, the ^{11}C-MET, few available data suggest a substantial diagnostic overlapping between this tracer and ^{18}F-DOPA, who have similar diagnostic accuracy. It is important to consider that the longer half-life of ^{18}F allows better clinical availability for ^{18}F-DOPA and also the application of various acquisition protocols and SUV studies. Moreover, ^{18}F-DOPA presents some similar features in diagnostic accuracy when compared to the other fluorinated amino acid tracers: ^{18}F-FLT and ^{18}F-FET, due to the common metabolic pathway of amino acid synthesis. There are two studies suggesting that ^{18}F-FET PET/CT seems to better depict the tumor lesions [24, 25]. Further larger studies in this field are also necessary.

It is necessary to reiterate that the actual gold standard of imaging in depicting brain tumor relapse still remains MRI: unfortunately, few available studies compared the performance of ^{18}F-DOPA PET/CT with MRI in the same population. Moreover, in the same examined population [13, 19] were studied patients with early diagnosed brain tumors or patients with suspicion of recurrence[11]. Nevertheless, all preliminary data suggested a substantial similarity between diagnostic efficacy of these tools: MRI offers a better spatial resolution limit and the chance of multi-planar evaluation [33, 34] while PET/CT with ^{18}F-DOPA could play a role in better depicting dubious findings allowing a metabolic characterization, especially in patients in whom a differential diagnosis between radiation necrosis versus tumor relapse is necessary [19, 26].

It is necessary to say that besides the low spatial resolution, of PET imaging, the ^{18}F-DOPA PET/CT, can detect tumor recurrence not clearly detectable on MRI and distinguish more accurately brain tumor relapse from brain necrosis [19], as shown in Figure 1.

In our clinical practice we often use MRI to evaluate suspected findings observed with ^{18}F-DOPA PET/CT because MRI can often detect small size relapses due to its higher resolution.

Our data, although in a limited number of cases, also suggest that both^{18}F-DOPA PET/CT and MRI technique can mutually support diagnosis [19, 35].

The recent availability of hybrid PET/MRI scanners allows for early stage detection of brain tumors. Simultaneous PET/MRI acquisition allows for complex panels and for multiple MR acquisitions with different contrast media during the PET study.

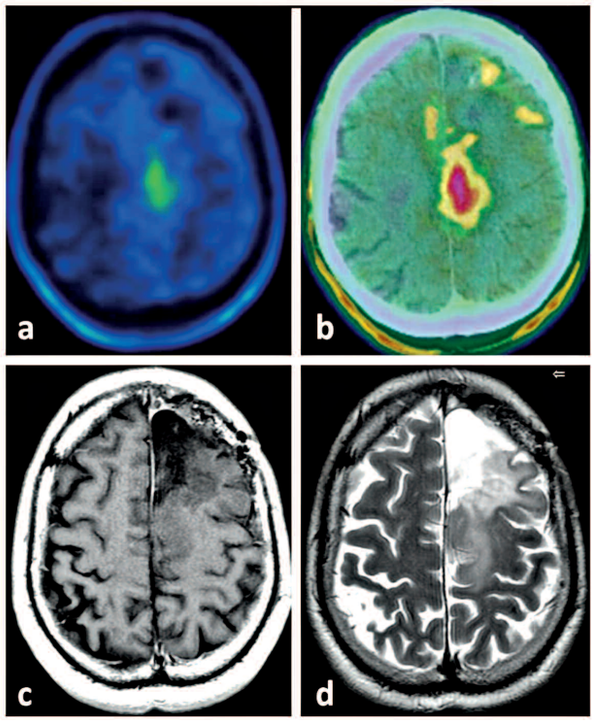

Figure 1. (a): Axial ^{18}F-DOPA PET and (b) PET/CT views show an area of high tracer uptake (SUVmax 4.6) in left sub-cortical, frontal, parietal region, corresponding to (c) mild hypointensity in T2-weighted MR axial image and (d) without significant contrast enhancement in T1-weighted post-contrast images. The patient was previously treated with surgical resection of a left temporal and parietal astrocytoma, two years before the scan (see the lacunar area in left frontal region, white arrow). In this patient ^{18}F-DOPA PET/CT showed better the recurrent brain tumor than MRI.

The best time to acquire ^{18}F-DOPA PET brain scan for oncologic studies is about 20min after tracer administration, since this time allows for the optimal visualization of tumoral cells, when using a PET/MRI scanner. The correlative MRI sequences can be acquired just after the intravenous administration of ^{18}F-DOPA, before the start of the PET scan, in order to reduce the artifacts due to the patient's movements of head and/or neck. Furthermore, novel hybrid PET/MRI scanners can acquire simoultaneously both PET and MRI images, minimizing the possibility of movement artifacts [36].

Of course, it is necessary to remember the importance of versatile co-operation with experienced radiologists or nuclear physicians experienced in the field of MRI, and also the importance of knowing anamnestic data of the patients.

Furthermore semi-quantitative measurement of the lesions is important to diagnose the tumor grade, as had already been cited for ^{18}F-FET [24].

As a future trend, it is noteworthy to underline that ^{18}F-DOPA is becoming a very versatile tracer, in neuro-oncological diseases and specifically in the detection of brain metastases. It is still necessary to verify some false positive sites of uptake with increased amino acidic turnover that can theoretically be detected in the brain during clinical practice [1], as is already known for other tracers [37, 38]. An interesting suggestion on this topic was provided by Gonzalez-Forero et al (2011) [39], who examined patients with suspicion of brain tumor recurrence or Parkinson's disease and incidentally observed uptake of ^{18}F-DOPA in a meningioma, a pineocytoma and an intrasinus hemangioma. Since they performed the PET scan with a dynamic acquisition of 90min, the authors observed an excellent relationship between the lesions and the healthy brain tissue, while the SUV max value of the malignant lesions was greater than that of the benign lesions. It has been previously reported that the kinetics of the ^{18}F-DOPA in malignant lesions show, an early maximum peak at 90min and a rapid descent curve, whereas in benign lesions the uptake progressively rises up to 90min [40] or in lesions with a low grade of malignancy. Therefore, further studies are needed to study the potential role of dynamic ^{18}F-DOPA PET/CT and to ensure the differential diagnosis of the malignant versus benign findings.

In conclusion, ^{18}F-DOPA seems to be a very promising PET tracer in the management of patients with suspicion of relapse of low or high grade tumors of the neuroepithelial tissue. However, future studies with larger populations are needed to assess its effective capability and compare it to the MRI studies (which are still now the gold standard) , in diagnosing brain tumors and their metastases.

The authors declare that they have no conflicts of interest.

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