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ORIGINAL ARTICLE

^{18}F-DOPA PET/CT in brain tumors: impact on multidisciplinary brain tumor board decisions

Olivier Humbert[1,2,3] · Véronique Bourg[4] · Lydiane Mondot[5] · Jocelyn Gal[6] · Pierre-Yves Bondiau[7] · Denys Fontaine[8] · Esma Saada-Bouzid[9] · Marie Paquet[1,2] · David Chardin[1] · Fabien Almairac[8] · Fanny Vandenbos[10] · Jacques Darcourt[1,2]

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Abstract

Purpose This study aimed to assess the therapeutic impact and diagnostic accuracy of ^{18}F-DOPA PET/CT in patients with glioblastoma or brain metastases.

Methods Patients with histologically proven glioblastoma or brain metastases were prospectively included in this monocentric clinical trial (IMOTEP). Patients were included either due to a clinical suspicion of relapse or to assess residual tumor infiltration after treatment. Multimodality brain MRI and ^{18}F-DOPA PET were performed. Patients' data were discussed during a Multidisciplinary Neuro-oncology Tumor Board (MNTB) meeting. The discussion was first based on clinical and MRI data, and an initial diagnosis and treatment plan were proposed. Secondly, a new discussion was conducted based on the overall imaging results, including ^{18}F-DOPA PET. A second diagnosis and therapeutic plan were proposed. A retrospective and definitive diagnosis was obtained after a 3-month follow-up and considered as the reference standard.

Results One hundred six cases were prospectively investigated by the MNTB. All patients with brain metastases ($N = 41$) had a clinical suspicion of recurrence. The addition of ^{18}F-DOPA PET data changed the diagnosis and treatment plan in 39.0% and 17.1% of patients' cases, respectively. Concerning patients with a suspicion of recurrent glioblastoma ($N = 12$), the implementation of ^{18}F-DOPA PET changed the diagnosis and treatment plan in 33.3% of cases. In patients evaluated to assess residual glioblastoma infiltration after treatment ($N = 53$), ^{18}F-DOPA PET data had a lower impact with only 5.7% (3/53) of diagnostic changes and 3.8% (2/53) of therapeutic plan changes. The definitive reference diagnosis was available in 98/106 patients. For patients with tumor recurrence suspicion, the adjunction of ^{18}F-DOPA PET increased the Younden's index from 0.44 to 0.53 in brain metastases and from 0.2 to 1.0 in glioblastoma, reflecting an increase in diagnostic accuracy.

Conclusion ^{18}F-DOPA PET has a significant impact on the management of patients with a suspicion of brain tumor recurrence, either glioblastoma or brain metastases, but a low impact when used to evaluate the residual glioblastoma infiltration after a first-line radio-chemotherapy or second-line bevacizumab.

Keywords 18F-DOPA · PET · Brain tumours · Amino acid · Therapeutic impact

✉ Olivier Humbert
ohumbert@unice.fr

[1] Department of Nuclear Medicine, Centre Antoine-Lacassagne, Université Côte d'Azur (UCA), 33 Avenue de Valombrose, 06100 Nice, France

[2] TIRO-UMR E 4320, UCA/CEA, Nice, France

[3] Clinical Research and Innovation Office, UCA, Nice, France

[4] Department of Neurology, Pasteur 2 University Hospital, UCA, Nice, France

[5] Department of Neuroradiology, Pasteur 2 University Hospital, UCA, Nice, France

[6] Department of Biostatistics, Centre Antoine-Lacassagne, UCA, Nice, France

[7] Department of Radiotherapy, Centre Antoine-Lacassagne, UCA, Nice, France

[8] Department of Neurosurgery, Pasteur 2 University Hospital, UCA, Nice, France

[9] Department of Medical Oncology, Centre Antoine-Lacassagne, UCA, Nice, France

[10] Central Laboratory of Pathology, Pasteur I University Hospital, UCA, Nice, France

Introduction

Gliomas and metastases are the most common malignant brain tumors. Brain metastases arise in 10–40% of systemic cancers with non-small cell lung cancer being the primary tumor in about half of the patients [1, 2]. In adult patients, primary brain tumors represent about 2% of all malignancies with glioblastomas accounting for 15% of them [3, 4]. Conventional treatments are based on different therapeutic modalities, which can be used alone or in association, including surgery, chemotherapy, and radiotherapy [5–8]. Nevertheless, patient's prognosis is poor, with different median survival times depending on the histologic type and primary tumor location. Median survival for glioblastoma, the most aggressive variant, is 16 months in patients treated with maximum safe resection, radiotherapy, and concurrent or adjuvant temozolomide [6–8].

Brain Magnetic Resonance Imaging (MRI) is the first-line imaging study to diagnose and monitor patients with brain tumors [9]. Different sequences are usually performed including T1-weighted contrast-enhanced multiplanar, T2-weighted as well as fluid-attenuated inversion recovery (FLAIR), diffusion, perfusion and spectroscopy [9–11]. However, the capability of brain MRI to depict brain tumor relapse and to assess treatment-induced changes (i.e. radiation necrosis or oedema) is limited [11, 12]. Indeed, contrast enhancement on MRI results from an increased blood–brain barrier permeability due to its breakdown is not specific of tumor invasion and can also be due to radionecrosis [13]. The sensitivity of MRI is also not optimal as infiltration by high-grade glioma can be found beyond the contrast-enhancement limits [14].

^{18}F-3,4-dihydroxyphenylalanine (^{18}F-DOPA) is a labeled amino-acid analog used for Positron Emission Tomography (PET) imaging. Its increased uptake in brain tumours is related to the over-expression of the amino-acid transporter LAT-1 in tumour cells and their vasculature [15–17]. This transport is not linked to the alteration of a blood–brain barrier [18]. ^{18}F-DOPA has been proposed for the imaging of primary and metastatic brain lesions, because of its high tumor–to–normal-brain background ratio [14, 19, 20]. Previous studies have evaluated the efficacy of ^{18}F-DOPA PET imaging in recently diagnosed or recurrent brain tumors through its technical and diagnostic performances. They demonstrated the good accuracy of ^{18}F-DOPA PET to image both low and high-grade brain tumors [11, 14, 21, 22]. Furthermore, Walter et al. showed that ^{18}F-DOPA PET changed the intended management in 41% of a series of primary and recurrent gliomas [23]. The study was conducted using a straightforward survey concerning the referring physician. More studies are needed to assess its effective capability to play a role in patient management and to assess its complementary value to MRI.

The aim of the present study was first to prospectively assess the impact of brain ^{18}F-DOPA PET studies on the therapeutic decision of a Multidisciplinary Neuro-oncology Tumor Board (MNTB) for patients with glioblastoma or brain metastases. Secondly, this study aimed to quantify the diagnostic accuracy improvement by the adjunction of ^{18}F-DOPA PET to the usual MRI criteria.

Methods

Population

From November 2013 to November 2015, patients were prospectively included in this monocentric clinical trial IMOTEP (n°ID-RCB:2013-A01123–42). This was an open, uncontrolled and non-randomized study to evaluate the contribution of ^{18}F-DOPA PET/Computed-Tomography (CT) imaging in the management of patients with primary or secondary brain tumors. The study was approved by the ethics committee and regulatory agencies. Informed consent was obtained from all individual participants included in the study. The inclusion criteria were histologically proven glioblastoma, either primary ('de novo') or secondary (progression from lower grade astrocytoma) or brain metastases. Regarding the patients included for an evaluation of residual glioblastoma after radiochemotherapy or anti-angiogenic therapy, the inclusions were done consecutively as they arrived to the neuro-oncology consultation. Regarding the patients with a suspected recurrence (either metastases or glioblastoma), they were included due to a doubt on clinical and/or MRI data. The exclusion criteria were: contraindication of brain MRI or ^{18}F-DOPA PET, vulnerable persons as defined in Article L1121–5 to −8 of the French Public Health Code, and refusal of written consent.

Image acquisition, reconstruction and interpretation

Two brain-centered imaging studies were performed: an MRI and a ^{18}F-DOPA PET. The time delay between these two imaging modalities did not exceed a 28-day-window.

1) MRI

MRI acquisitions were performed on a 1.5 T MR scanner (Signa horizon LX, GE Healthcare, Milwaukee, Wisconsin) 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 to assess vasogenic oedema and infiltrating tumor; Diffusion-Weighted Imaging (DWI) sequences (B = 1000) to evaluate tumor cellularty; spin-echo planar Dynamic

Susceptibility Contrast Perfusion-Weighted Imaging (DSC-PWI) as a surrogate marker for angiogenesis; and a 3D T1-weighed GRE contast-enhanced sequence (Dotarem®, 0.1 mmol/kg) to evaluate gadolinium enhancement. Spectroscopy was performed in most MRI exams (93/106) to measure tumor metabolites. The MRI was interpreted by a radiologist expert in brain tumors, using the whole set of sequences and GE software (Advantage Workstation 4.6).

2) ^{18}F-DOPA PET/CT

Patients underwent a protein fast for at least 4 h. One hour prior to the injection of ^{18}F-DOPA, 100 mg of Carbidopa was orally taken to reduce the activity of the peripheral DOPA-decarboxylase. Twenty minutes after the injection of 2 MBq/Kg of ^{18}F-DOPA, a dedicated CT scan of the brain (120 kV, 80 mAs, 3 mm slice collimation) was performed, followed by a brain-centered static 3D PET acquisition of 10 min (Biograph mCT, Siemens healthcare, Erlangen, Germany). PET images were reconstructed using the OSEM iterative algorithm (5 iterations, 24 subsets), with scatter and attenuation correction but without point-spread function correction. For visual reading, ^{18}F-DOPA PET were systematically fused to contrast-enhanced T1 weighted MRI sequences. The image matching process was carried out using trilinear interpolation, rigid matching and using a mutual information algorithm with the SyngoVia software, Siemens. Images were qualitatively analyzed using the visual 4-point scale proposed by Lizarraga et al. (Fig. 1) [24]:

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 were considered as negative, whereas scores 2 and 3 were considered as positive for recurrence or residual tumor infiltration.

Tumor board design

Patients' clinical records were presented and discussed during the weekly MNTB of our University Hospital including neuro-oncologists, neuro-surgeons, radiologists, pathologists, radiotherapists and nuclear physicians. According to the protocol, the MNTB discussion was systematically organized as followed:

- Step 1: Discussion based on clinical data and the MRI images (all sequences) without the intervention of the nuclear physician. Following this discussion, a first diagnosis (diag.1) and treatment plan (treat.1) were issued. The treatment options of the therapeutic proposal were: therapeutic abstention (including supportive care), continuation with the same treatment modality, new treatment modality. Treatment modalities included radiation, chemotherapy, radiation with chemotherapy and surgery. The confidence level of this first therapeutic proposal was assessed using a first confidence score (CS1).
- Step 2: A second case discussion based on the overall imaging results, including ^{18}F-DOPA PET, was conducted. Following this discussion, a second diagnosis (diag.2)

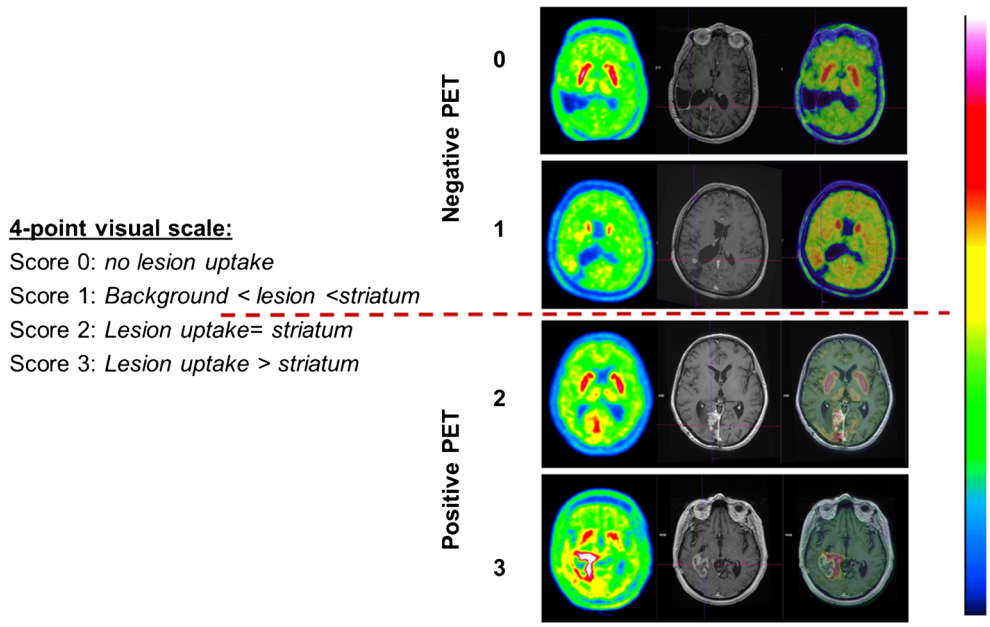

Fig. 1 PET visual interpretation. ^{18}F-DOPA PET images on the *left*; T1-weighed MRI sequence with gadolinium contrast enhancement in the *middle*; ^{18}F-DOPA PET/MR image fusion on the *right*. ^{18}F-DOPA PET images were interpreted with the 4-point visual scale: the striatum uptake was used as an internal reference and the maximum colour scale set on the striatum

and therapeutic plan (treat.2) were issued. As for step 1, the treatment proposal was a three-way choice, reflecting the main therapeutic possibilities: therapeutic abstention, continuation of the same treatment modality, new treatment modality. The confidence level of this proposal was assessed using a second confidence score (CS2). In case of no therapeutic proposal changes, confidence scores 1 and 2 were compared. The confidence level was decreased, unchanged or increased.

Retrospective final diagnosis 3 months after CPR

This final diagnosis was based on pathological data (in case of biopsy or surgery performed) or, if not available, on the clinical follow up and on the imaging data obtained up to 3 months after the MNTB. This definitive diagnosis was taken as a reference standard and compared with the initially proposed diagnoses (diag.1 and diag.2).

Statistical analyses

The required number of cases to be evaluated in MNTB was calculated to be 85 (taking into account about 5% of misincluded patients, lost to follow-up or withdrawn from the study). Data entry and management were performed on the capture system (Ennov Clinical®). Statistical analyses were performed with 5% alpha risk using SAS 9.4 and R.3.2.2 software. Qualitative data were presented as absolute frequencies and percentages. The quantitative data were presented in mean value and standard deviation, or median and extreme values. The sensibility, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and Youden's Index (summarizing the performance of the diagnosis) of diag.1 and diag.2 to detect tumor recurrence or progression to treatment were calculated. Statistical analyses were performed with 5% alpha risk using SAS 9.4 and R.3.2.2 software.

Results

Overall population

Seventy-eight patients were prospectively included. The mean patient age was 60.5 ± 11.3 years [range: 36–89]. Since a patient's record could be discussed up to three times by the MNTB in the protocol during the one-year follow-up whenever his clinical status required a new therapeutic decision, a total of 106 patient cases were investigated by the MNTB. The mean delay between MRI and PET was 11.1 ± 8.8 days [range: 0–28]. Using the 4-point scale for PET interpretation, 28 patients had a negative ^{18}F-DOPA PET result (visual score 0 or 1). In this group, the lesion SUV_{max} and SUV_{mean} tumour to striatum ratios were 3.34 ± 0.95 and 0.78 ± 0.18, respectively. Sixty-eight patients had a positive PET result (visual score 2 or 3). In this group, the lesion SUV_{max} and SUV_{mean} tumour to striatum ratios were 4.79 ± 1.3 and 1.12 ± 0.25, respectively. The final retrospective diagnosis was available in 98/106 patient's cases: ten based on pathological results and 88 based on clinical and imaging follow-up at 3 months (Table 1).

Patients with brain metastases (*N* = 41/106)

The indication was a clinical suspicion of recurrence in all cases (41/41). In most of these cases, the primary was lung cancer (51.5%).

1) Diagnostic impact of 18F-DOPA (Table 2)

Diagnosis 1 and diagnosis 2, obtained respectively before and after the consideration of the ^{18}F-DOPA PET results, are given in Table 2. The diagnosis was changed in 39.0% of cases (16/41) by the implementation of ^{18}F-DOPA PET data, mainly resulting from a higher number of positive diagnosis of recurrence (39.0 to 70.7% of the cases).

2) Therapeutic impact of ^{18}F-DOPA (Tables 3 and 4)

The treatment plan was changed in 17.1% of patients (7/41), corresponding to an upgrade from therapeutic abstention to treatment for all of them.

If no therapeutic changes were proposed (*N* = 34), the confidence index of the therapeutic decision was decreased, unchanged and increased in 26.5% (9/34), 70.6% (24/34) and 2.9% (1/34) of cases, respectively. In patients whose confidence index decreased, five had no recurrence at the final diagnosis, two had recurrence and two did not have a final diagnostic confirmation.

3) Diagnostic accuracy

The accuracies of diag.1 (diagnosis 1) and diag.2 (diagnosis 2) to predict the definitive diagnosis are described

Table 1 Number of patients with a final diagnosis based on pathological data or on a 3-month follow-up

Diagnosis	Final diagnosis based on pathological data (N)	final diagnosis based on a 3-month follow-up (N)
Glioblastoma	5	60
Brain metastases	5	28
Total	10	88

Table 2 Description of diagnosis 1 and diagnosis 2

Indication	Diagnosis 1 *N* (%)	Diagnosis 2 *N* (%)
Metastases (N = 41)		
No recurrence	25 (61.0)	11 (26.8)
Recurrence	16 (39.0)	29 (70.7)
Inconclusive	0	1 (2.4)
Glioblastoma, Suspicion of recurrence (N = 12)		
No recurrence	4 (33.3)	2 (16.7)
Recurrence	8 (66.7)	10 (83.3)
Inconclusive	0 (0.0)	0 (0.0)
Glioblastoma, Residual disease assessment (N = 53)		
Stable	7 (13.2)	8 (15.1)
Response	16 (30.2)	16 (30.2)
Progression	30 (56.6)	29 (54.7)

in Table 5 and Fig. 2. The sensibility, specificity, PPV, NPV, and Youden's index of diag.1, based on clinical data and MRI, were 56.2%, 88.2%, 81.8%, 68.2% and 0.44, respectively. In comparison, those of diag.2 (after the consideration of ^{18}F-DOPA PET results) were 100%, 52.9%, 66.7%, 100% and 0.53, respectively. Thus, after the adjunction of ^{18}F-DOPA PET results, the NPV of brain imaging to detect recurrence increased from 68.2 to 100%, but the PPV decreased from 81.8 to 66.7%. The Youden's index, reflecting the diagnostic accuracy of the two diagnoses, increased from 0.44 to 0.53.

Patients with glioblastoma (*N* = 65/106)

18.5% (12/65) were included with a clinical suspicion of recurrence and 81.5% (53/65) for a residual tumor assessment after treatment. Regarding the therapeutic modality in this last group of patients:

- 66% (35/53) were evaluated after a first-line concomitant radio-chemotherapy (STUPP protocol) associating radiotherapy (60 Gy) and temozolomide followed by temozolimide alone. The evaluation was done during the temozolomide maintenance period.
- 34% (18/53) were evaluated to assess tumor residual disease to a second line treatment with bevacizumab alone (10 mg/kg every 14 days)

1) Diagnostic impact of ^{18}F-DOPA (Table 2)

Diag1 and diag.2, obtained respectively before and after the consideration of the ^{18}F-DOPA PET results, are given in Table 2.

- *Patients with a suspicion of recurrence*: The diagnosis was changed in 33.3% of cases (4/12).
- *Patients studied for residual tumor assessment after treatment*: ^{18}F-DOPA PET had a lower diagnostic impact with only 5.7% (3/53) of changes. These diagnostic changes involved patients previously treated with first-line concomitant radio-chemotherapy

2) Therapeutic impact of ^{18}F-DOPA (Tables 3 and 4)

- *Patients with a suspicion of recurrence:* The treatment plan was changed in 33.3% (4/12) with an upgrading to new treatment modality for 25.0% (3/12) of them. ^{18}F-DOPA downgraded the therapeutic proposal from treatment to therapeutic abstention in the remaining patients. When no therapeutic change was proposed, the confidence index of the therapeutic decision was unchanged and increased in both 50.0% of cases (both 4/8).

Table 3 Description of treatment plan 1 and treatment plan 2

Indication	Therapeutic proposal 1 *n* (%)	Therapeutic proposal 2 *n* (%)
Metastases (N = 41)		
Therapeutic abstention	24 (58.5)	17 (41.5)
Continuation of the same treatment modality	2 (4.9)	2 (4.9)
New treatment modality	15 (36.6)	22 (53.6)
Glioblastoma, Suspicion of recurrence (N = 12)		
Therapeutic abstention	3 (25.0)	3 (25.0)
Continuation of the same treatment modality	3 (25.0)	1 (8.3)
New treatment modality	6 (50.0)	8 (66.7)
Glioblastoma, Residual disease assessment (N = 53)		
Therapeutic abstention	7 (13.2)	6 (11.3)
Continuation of the same treatment modality	27 (50.9)	26 (50.0)
New treatment modality	19 (35.8)	21 (39.6)

Table 4 Changes in patient treatment

Indication	Changes in treatment plan *n* (%)
Metastases (N = 41)	
From new treatment modality to therapeutic abstention	0 (0.0)
From therapeutic abstention to treatment	7 (17.1)
From continuation of the same treatment modality to new treatment modality	0 (0.0)
Glioblastoma, Suspicion of recurrence (N = 12)	
From new treatment modality to therapeutic abstention	1 (8.3)
From therapeutic abstention to treatment	1 (8.3)
From continuation of the same treatment modality to new treatment modality	2 (16.7)
Glioblastoma, Residual disease assessment (N = 53)	
From continuation of the same treatment modality to new treatment modality	1 (1.9)
From therapeutic abstention to treatment	1 (1.9)

- *Patients studied for residual tumor assessment:* the therapeutic plan was changed in 3.8% (2/53), corresponding to an upgrading to new treatment modality. When no therapeutic change was proposed, the confidence index was decreased, unchanged and increased in, respectively, 2.0% (1/51), 84.3% (43/51) and 13.7% (7/51) of cases, respectively.

3) Diagnostic accuracy

- *Patients with a suspicion of recurrence*: The sensibility, specificity, PPV and NPV of diag.1, based on clinical data and MRI, were 70.0%, 50.0%, 87.5% and 25.0%. In comparison, those of diag.2 (after the consideration of ^{18}F-DOPA PET results) were all calculated at 100%. The Youden's index, reflecting the diagnostic accuracy of the two diagnoses, increased from 0.2 to 1.0.
- *Patients studied for residual tumor assessment:* the sensibility, specificity, PPV, NPV, and Youden's Index of diag.1, were 92.3%, 77.8%, 80.0%, 91.3% and 0.70, respectively. The sensibility, specificity, PPV, NPV and Youden's Index of diag.2 were 92.3%, 81.5%, 82.8%, 91.7% and 0.74, respectively. Thus, after the adjunction of ^{18}F-DOPA PET results, the Youden's index of brain imaging increased only slightly from 0.70 to 0.74.

Discussion

The assessment of tumor metabolism with amino-acid PET can detect high- and low-grade brain tumors independently of the blood–brain barrier breakdown. Thus, it is complementary to MRI, the current imaging gold-standard [9, 18]. Previous studies have demonstrated the usefulness of amino-acid PET for the diagnosis, treatment monitoring, and prognostic evaluation of patients with high grade gliomas and brain metastases [21, 22, 25–28]. For example, ^{18}F-DOPA can accurately differentiate glioma recurrence from treatment-induced changes (e.g., pseudo-progression, radionecrosis) [12, 21, 22]. The recently published neuro-oncology recommendations concerning the clinical use of PET imaging in gliomas have concluded that future

Table 5 Confrontation between the baseline (Diag.1 and Diag.2) and the definitive diagnosis

Parameters	Overall		Metastases: suspicion of recurrence		Glioblastoma: suspicion of recurrence		Glioblastoma: residual disease assessment	
	Diag.1	Diag.2	Diag.1	Diag.2	Diag.1	Diag.2	Diag.1	Diag.2
TP	40	50	9	16	7	10	24	24
FP	9	13	2	8	1	0	6	5
TN	37	33	15	9	1	2	21	22
FN	12	2	7	0	3	0	2	2
Sensitivity	76.9	96.1	56.2	100	70.0	100	92.3	92.3
Specificity	80.4	71.7	88.2	52.9	50.0	100	77.8	81.5
PPV	81.6	79.4	81.8	66.7	87.5	100	80.0	82.8
NPV	75.5	94.3	68.2	100	25.0	100	91.3	91.7
Accuracy	78.6	84.7	72.7	75.6	66.7	100	84.9	86.8
Youden's index	0.57	0.68	0.44	0.53	0.20	1.0	0.70	0.74

TP True Positive, *FP* False Positive, *TN* True Negative, *FN* False Negative, *PPV* Positive Predictive Value, *NPV* Negative Predictive Value, *Diag.1* diagnosis 1, *Diag.2* diagnosis 2

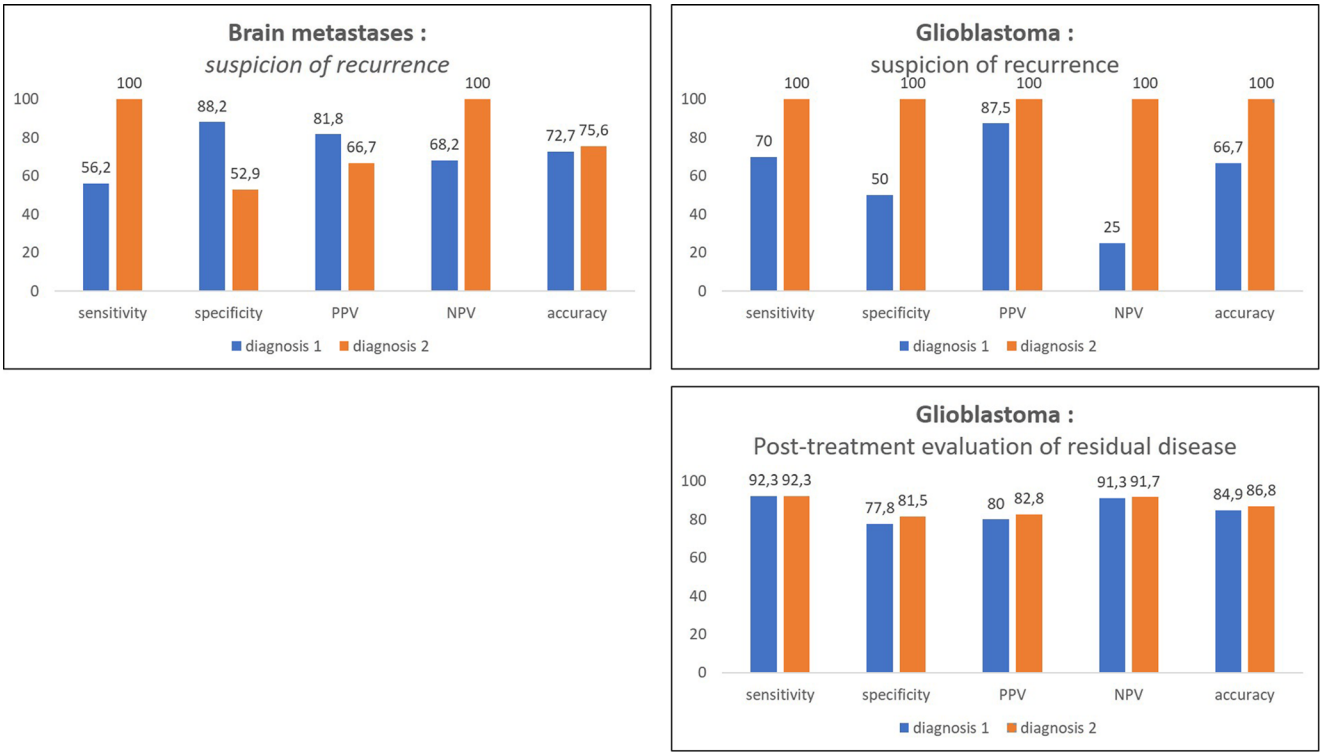

Fig. 2 Description of diagnostic tests, before (diagnosis 1) and after (diagnosis 2) ^{18}F-DOPA PET

prospective clinical studies should consider the use of amino-acid PET as an imaging modality for gliomas [29]. However, they have also stated that further studies were needed to evaluate the efficacy of ^{18}F-DOPA PET in the promotion of patient health, and its cost-effectiveness in patient care. The present prospective clinical research investigated the clinical role of PET, as a complement to MRI, in two different brain tumor pathologies: glioblastoma and brain metastases. It demonstrated a significant therapeutic impact of ^{18}F-DOPA PET in patient management.

Brain metastases

The clinical setting was tumor recurrence suspicion for all patients with brain metastases. We found a clinical value for the adjunction of ^{18}F-DOPA PET to MRI. The consideration of ^{18}F-DOPA PET results changed the diagnosis in about 40% of patients, mostly from "no recurrence" to "recurrence". The treatment plan was changed in 17% of cases. When the treatment was unchanged, it is worth noting that the confidence index of the therapeutic decision decreased in 26% of patients. This is explained by discordant imaging results between MRI and PET, with the MNTB rather favouring the MRI than the PET results to guide the therapeutic strategy.

Finally, the diagnostic accuracy was improved after the implementation of ^{18}F-DOPA PET, due to the decrease of false negative diag.1, correctly reclassified as true positive by PET at diag.2. This is in accordance with the study of Cicone et al., which also demonstrated a higher accuracy of ^{18}F-DOPA, compared to perfusion-MRI, to detect true brain metastatic recurrence after stereotactic radiosurgery [12].

The main benefit of ^{18}F-DOPA PET in this setting was that a negative result could completely exclude tumor recurrence. Nonetheless, a main drawback of ^{18}F-DOPA PET was a decrease of the positive predictive value of the diagnosis. Among patients with false positive results at diag.2, two patients were surgically verified since both PET and MRI were positive for recurrence. The pathology diagnosis was radionecrosis but immunostaining revealed a significant expression of LAT1 by the activated astrocytes of this lesion. This finding questions the specificity of the tumoral expression of LAT1 in that situation as already pointed out by Sala et al. [30].

Thus, the high negative predictive value of the diagnosis after ^{18}F-DOPA PET is useful to rule-out recurrence. However, it induces some false positive cases. New PET criteria, more stringent that the Lizarraga scale, may be useful to more accurately assess brain metastases recurrence. Cicone et al. have also previously suggested that PET data are to be analysed semi-quantitatively, as visual scores provide inferior performance [12].

Glioblastoma

Results differ according to the clinical setting: either detection of tumor recurrence or systematic residual tumor assessment after treatment.

- **Suspicion of recurrence**

Although few patients belonged to this group, we found a high clinical value of the adjunction of ^{18}F-DOPA PET to MRI. The diagnosis was changed in one third of patients, mostly from "no recurrence" to "recurrence". These patients had either no suspicious abnormalities on multimodality MRI or contrast enhanced lesions interpreted as pseudo-progression (treatment related changes without recurrence). The corresponding ^{18}F-DOPA PET revealed a pathological uptake and the MNTB reclassified the diagnosis as recurrence. The ability of labelled amino-acids PET to help diagnosing pseudo-progression has already been shown [31–34].

The consideration of ^{18}F-DOPA PET results also changed the treatment plan in one third of the cases. When the treatment proposition was unchanged, it is worth noting that the confidence index of the therapeutic decision was increased in half of the patients. Finally, the diagnostic accuracy was strongly improved after the implementation of ^{18}F-DOPA PET and reached a perfect diagnostic accuracy in this small subset of patients.

In 11 patients with recurrent glioma, Ledezma et al. have also previously reported that ^{18}F-DOPA PET/CT had a sensitivity of 100%, while MRI had a sensibility of 82%, paralleling our results [14]. The diagnostic accuracy in detecting brain tumor relapses was substantially improved by the adjunction of PET/CT, due to a high improvement of the negative predictive value. The above findings were also prospectively confirmed by Karunanithi et al. in a population of 35 patients with recurrent glioma [22]. The sensitivity, specificity and accuracy of MRI to detect recurrent glioma were 92.3%, 44.4% and 80%, respectively. Those of ^{18}F-DOPA PET/CT were 100%, 88.9% and 97.1% respectively. ^{18}F-DOPA PET/CT was more specific than MRI for both high-grade and low-grade gliomas.

Few studies have previously investigated the therapeutic impact of the adjunction of ^{18}F-DOPA PET/CT to the current imaging strategy. Walter et al. have prospectively included 58 patients, most of them with a suspicion of recurrent glioma [23]. Their results were based on a pre and post-DOPA PET questionnaire sent to the referring physician. ^{18}F-DOPA PET changed the final therapeutic management (effective therapeutic changes) in 31% of patients, which is very close to our results (33.3% for patients with a suspicion of recurrent glioblastoma). However, there are differences between the two studies. In our case, all patients benefited from a multiparametric brain MRI, including advanced imaging sequences (DSC-PWI, DWI and spectroscopy), which could have reduced the diagnostic impact of ^{18}F-DOPA PET compared with study using only conventional MRI sequences. Furthermore, we only considered major therapeutic management changes, such as a modification in treatment plan category (i.e. from surgery to chemotherapy or to therapeutic abstention). Minor treatment changes were not recorded. Finally, our study investigated the impact of ^{18}F-DOPA PET in the decision process of a multidisciplinary brain tumor board rather than of a single referring physician (Fig. 3)..

- **Residual tumor assessment after Stupp protocol or bevacizumab therapy**

In this clinical setting, the clinical benefit of ^{18}F-DOPA PET appears to be low with very few changes in patient diagnosis and therapeutic management. Furthermore, the improvement of diagnostic accuracy (Youden's index) after the implementation of ^{18}F-DOPA PET was not significant. This may be explained by the good performances of MRI to identify progression under treatment. It is worth noting that the confidence index of the therapeutic decision increased in a significant number of patients (13.7%) and rarely decreased after consideration of PET results. This may be explained by PET confirming a more questionable MRI result.

In contrast, previous studies have demonstrated that radiolabelled amino-acid PET can help monitor treatment to response, in particular for differentiating MRI pseudo-response from progression to anti-angiogenic treatments [27, 35, 36]. But most of these previous studies aimed to evaluate tumor early response to treatment, performing baseline and interim PET. The low impact on patient management in this study may be explained by the significantly different clinical setting: we used PET to assess residual tumor infiltration at the end of treatment, without using a baseline PET for comparison.

Advantages and limits of the study

In their study, Walter et al. mentioned that the reported impact on patients' management may have been biased toward favouring PET [23]. Indeed, the surveyed physicians were regular PET users and were probably convinced of the benefit of this imaging modality. In contrast, the present study is less prone to this bias because the decision of treatment changes was assessed during a multidisciplinary MNTB with surgeons, radiotherapists, oncologists and imaging specialists, for whom decisions were made more objectively. Another advantage is that we compared the two baseline imaging diagnoses with the definitive diagnosis based on pathological results or on the collection of clinical and imaging data carried out three months later. Thus, we could evaluate the accuracy of the baseline diagnosis and the resulting therapeutic decision.

Various amino-acid PET tracers have been developed and evaluated in the setting of brain tumor imaging [37–39]. We used ^{18}F-DOPA for several reasons. Firstly, ^{18}F-DOPA is approved and reimbursed for characterization of brain tumor in some European countries, including France. Secondly, ^{18}F-DOPA is a versatile tracer, with oncological and non-oncological indications, thus enabling the nuclear physician to image enough patients for a full ^{18}F-DOPA PET session [21, 40, 41]. This is a real logistic advantage in clinical

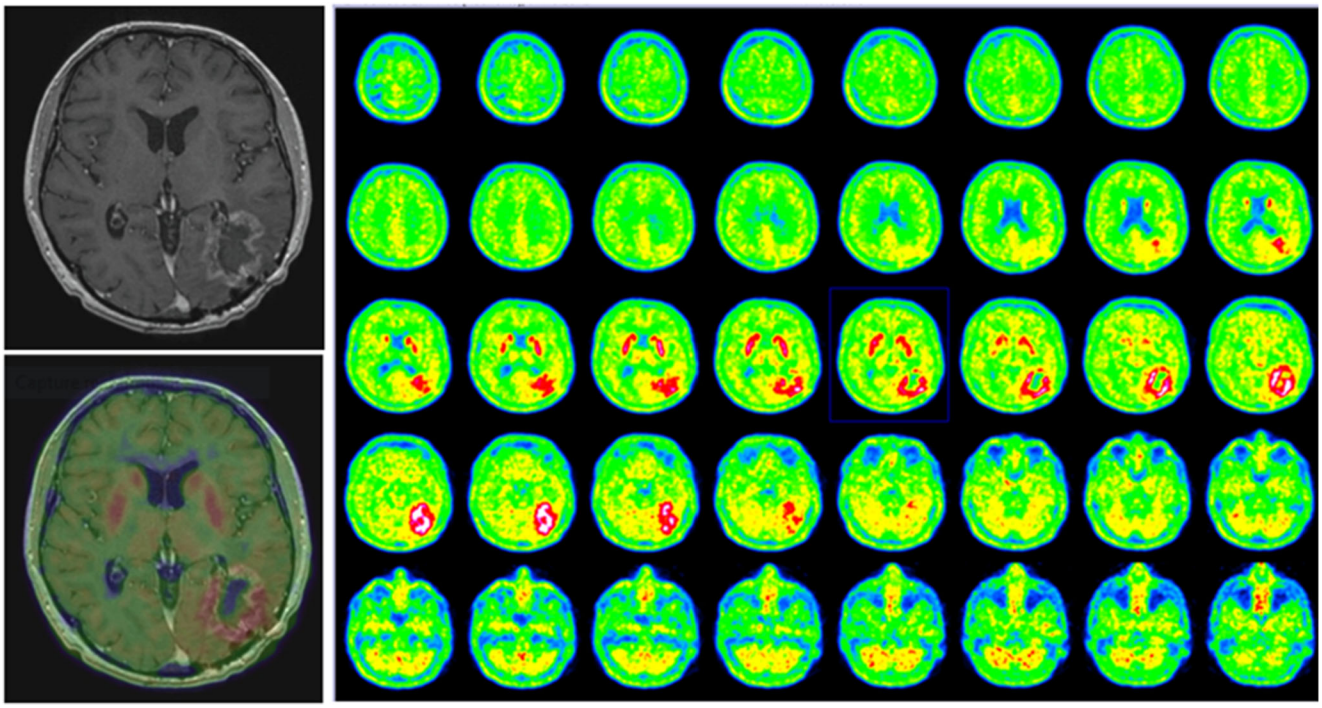

Fig. 3 Patient's case. A 60-year-old man with a history of left parietal glioblastoma who benefited from a complete surgical resection followed by radio-chemotherapy. Eleven months later he had a clinical suspicion of recurrence. But based on patient history (MGMT methylated) and MRI data (morphological sequences, perfusion and spectrometry), the first MNTB proposed pseudo-progression as diag. 1. and therapeutic abstention. Because PET images show a high ^{18}F-FDOPA uptake in the periphery of the necrotic lesion (level 3 score), the second MNTB proposed recurrence as a diag. 2 (diagnostic change) as well as surgery (therapeutic change). Pathology confirmed a centrally necrotic lesion surrounded by glioblastoma recurrence. Upper left: T1 contrast enhanced MRI. Right: 18F-FDOPA PET images. Lower left: 18F-FDOPA image fused with MRI

practice. Furthermore, the internal reference offered by the physiological striatal uptake offers the possibility of a visual reading and scaling which makes image reading very intuitive in a multidisciplinary environment [24]. Which amino acid PET tracer is optimal in this clinical setting is still debated. However, the feasibility and usefulness of ^{11}C-MET, ^{18}F-FET, or ^{18}F-FDOPA PET for treatment assessment after chemo-radiotherapy or bevacizumab have been demonstrated in different studies, primarily in WHO grades III/IV gliomas [29]. These three amino acid PET tracers have been demonstrated to be more accurate than conventional MRI for the differentiation between treatment-related changes and true recurrent glioma [22, 31, 34, 35].

Carbidopa is a known aromatic amino acid decarboxylase inhibitor, affecting the conversion of L-DOPA to dopamine in extra-cerebral tissues. It is demonstrated that pre-treatment with carbidopa improves imaging of the striatum by preventing early decarboxylation of ^{18}F-DOPA to ^{18}F-dopamine outside the brain. Carbidopa is also used to increase ^{18}F-DOPA uptake by tumor cells in the imaging of NETs [42]. In brain tumor imaging, the impact of carbidopa on lesion uptake is more debated since few studies addressed this issue with conflicting results [21, 39, 43]. Carbidopa was administrated in the present study; however, it is probably not mandatory for ^{18}F-DOPA PET brain tumor imaging and it very unlikely affects the clinical results of our study.

The main limitation of the present study was the heterogeneity of tumor types (glioblastoma or brain metastases) and clinical settings (suspicion of recurrence/ post-treatment evaluation). However, this reflects the clinical practice. Concerning MRI interpretation, The Response Assessment in Neuro-oncology (RANO) criteria were not strictly applied because the neuroradiologist also referred to DCS-PWI, DWI and spectroscopy sequences [44].

In the clinical setting of tumor residual disease assessment, MRI and ^{18}F-DOPA PET studies were programmed simultaneously. In many instances MNTB considered that MRI data were sufficient for a decision. Therefore, the added value of ^{18}F-DOPA PET in this setting probably would have been higher if it were only performed when MR was doubtful.

The mean time delay between both imaging modalities was 11.1 ± 8.8 days. For the few patients with a delay approaching 28 days, the diagnostic accuracy may have tended to favour PET as it was usually performed after MRI.

The current gold standard brain tumors diagnosis is histology. In our study, this gold standard was available only in ten patients. Therefore, we mainly used the clinical and imaging follow-up at 3 months to assess the final retrospective diagnosis.

Lastly, concerning gliomas, this study did not take into account molecular characteristics as proposed by the World

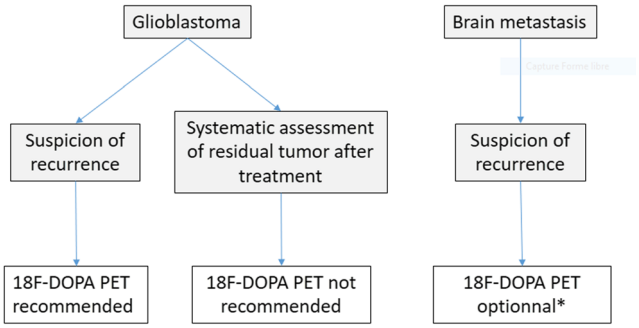

Fig. 4 Algorithm proposal for the use of ^{18}F-DOPA PET in brain tumors management. *Only in case of a doubtful positive result on MRI, based on the high negative predictive value of ^{18}F-DOPA PET

Health Organization 2016 classification, distinguishing IDH-wildtype and IDH-mutant glioblastoma. It has been established that molecular characteristics have an impact on amino-acid uptake [45, 46]; however, this is probably more relevant for the initial diagnosis than for the follow-up.

In conclusion, the current imaging gold standard for the diagnosis of brain tumour relapse and the evaluation of treatment response is MRI. However, the present study shows that MRI and ^{18}F-DOPA PET are complementary for early recurrence detection. In this setting, the added information brought by PET has a significant impact on patient management, leading the MNTB to change treatment plan in one third of patients with glioblastoma and 17% of patients with brain metastases. In contrast, the therapeutic impact is not significant for the evaluation of residual disease after a first-line radio-chemotherapy or second-line bevacizumab. Based on our results, an algorithm for the use of ^{18}F-DOPA PET in brain tumors can be proposed (Fig. 4).

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Compliance with ethical standards

Conflict of interest All authors of this manuscript declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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