Effects of carbidopa premedication on ^{18}F -FDOPA PET imaging of brain tumors: a static, dynamic and radiomics analysis

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Research Article

Keywords: DOPA, PET, carbidopa, glioma, dynamic, radiomics

Posted Date: July 26th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-732194/v1>

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Abstract

Purpose

This study aims to determine the impact of carbidopa premedication on static, dynamic and radiomics parameters of ^{18}F -FDOPA PET imaging in brain tumors.

Material and Methods

The study included 54 patients that underwent ^{18}F -FDOPA PET imaging for newly diagnosed gliomas. Among these, 18 patients received 100 mg of carbidopa. SUV parameters and 105 radiomics features were extracted from the static images. Dynamic data were available for 41 patients. Time to Peak (TTP) values were extracted from dynamic acquisitions. These parameters were obtained from volumes of interest in healthy brain as well as tumors. Simulation of the effects of carbidopa premedication on TTP values were also generated.

Results

All static and TTP dynamic parameters were significantly increased in healthy brain regions of premedicated patients ($\Delta\text{SUV}_{\text{mean}} = +53\%$, $\Delta\text{TTP} = +48\%$, $p < 0.001$). Furthermore, carbidopa impacted 81% of radiomics features, of which 92% correlated with SUV_{mean} (absolute correlation coefficient ≥ 0.4). In tumors, premedication with carbidopa was an independent predictor of SUV_{mean} ($\Delta\text{SUV}_{\text{mean}} = +52\%$, $p < 0.001$) and TTP ($\Delta\text{TTP} = +24\%$, $p = 0.025$). Interestingly, all parameters were no longer significantly modified by carbidopa premedication when using tumor-to-healthy-brain image and TAC ratios. Simulated data confirmed that carbidopa leads to an increase in tumor TTP values which is corrected by using these ratios.

Conclusion

In ^{18}F -FDOPA PET brain imaging, carbidopa induces an increase of similar magnitude in SUV, SUV-dependent radiomics and TTP dynamic parameters in healthy brain and tumor regions which are compensated for after using the tumor-to-healthy-brain image and TAC ratios which is an important point for multicentric studies harmonization.

Declarations

Ethics approval and consent to participate: All procedures in studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the latest amendments of the 1964 Helsinki declaration or comparable ethical standards. Written informed consent was obtained from all individual participants included in the study. The institutional ethics committee (Comité d’Ethique du CHRU de Nancy - FRANCE) approved the evaluation of retrospective patient data on August 26, 2020. The trial was registered at ClinicalTrials.gov (NCT04469244).

Consent for publication: Not applicable

Availability of data and materials: All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests: All authors declare that they have no competing interests.

Funding: None

Author’s contributions: All authors participated either in the: 1) Study conception and design or analysis and interpretation of the data, or both: (MB, TZ, GH, AV); 2) The drafting of the manuscript or revising it critically for important intellectual content: (MB, TZ, PYM, AV); 3) Final approval of the submitted manuscript: (LT, MB, FR AV).

Acknowledgements: The authors thank Petra Neufing for critical review of the manuscript.

Introduction

L-3,4-dihydroxy-6- ^{18}F -fluoro-phenyl-alanine (^{18}F -FDOPA) is a PET amino-acid radiotracer that has been used to assess gliomas for over 20 years [1]. The PET-RANO group (Response Assessment in Neuro-Oncology) recommends its use at the primary diagnosis, for monitoring disease and therapy, and for diagnosing tumor recurrence [2–4].

^{18}F -FDOPA has a relatively high specificity for gliomas, conferred by its ability to cross an intact blood-brain barrier and the overexpression of Large Amino-acid Transporters (LATs) in tumors [5,6], making it a useful adjunct to contrast enhanced brain MRI which remains the gold standard for the diagnostic assessment of gliomas.

Carbidopa (L-a-hydrazino-a-methyl-b-(3,4-dihydroxyphenyl)propionic acid) is a peripheral inhibitor of aromatic amino acid decarboxylase. Its use as a premedication therefore results in increased plasma concentrations of ^{18}F -FDOPA and of its metabolite ^{18}F -OMFD (3-O-methyl-6-[^{18}F]fluoro-L-DOPA) [7]. As

^{18}F -FDOPA K1 [8] and the net influx rate constant Ki [7] are not affected by this premedication, carbidopa pretreatment leads to an increase of radiotracer uptake in both healthy brain and glioma [9]. The proportion of uptake increase in these two structures and the effects of carbidopa premedication on the radiomics parameters as well as the dynamic analysis nevertheless remain to be determined. To date only one study consisting of two patients premedicated with 200 mg of carbidopa showed an average 50% increase in uptake in the cerebellum, striatum and the tumor, based on acquisitions obtained 15 to 25 min post injection [9].

In contrast to movement disorders PET imaging [10], international guidelines do not recommend administering carbidopa before ^{18}F -FDOPA PET for brain tumor imaging, solely based on the fact that most of the published studies do not use it. There is currently no evidence-based data to determine whether carbidopa should be used in the clinical setting of brain tumor imaging, particularly in the current era of routine semi-quantitative analyses [3].

The objective of this study is therefore to determine the impact of carbidopa premedication on static, radiomics and dynamic parameters in brain tumor ^{18}F -FDOPA PET imaging.

Materials And Methods

Population and ^{18}F -FDOPA PET imaging

We retrospectively selected newly diagnosed glioma patients, classified according to the WHO 2016 classification [11], who underwent an ^{18}F -FDOPA PET at the CHRU of Nancy between January 2013 and October 2017. Premedication data was available for all patients included in the study and depended on the routine examination protocol performed; patients analyzed from March 2016 to October 2017 were premedicated with carbidopa and patients analyzed from January 2013 to February 2016 were not premedicated prior to PET imaging. The data evaluation process was approved by the local ethics committee (Comité d'Éthique du CHRU de Nancy) on August 26, 2020. The trial was registered at Clinical Trials.gov (NCT04469244). This research complied with the principles of the Declaration of Helsinki. Informed consent was obtained from all individuals included in the study.

^{18}F -FDOPA PET-computed tomography (CT) scans were performed on a Biograph hybrid system involving a six-detector CT for attenuation correction (Biograph 6 True Point, SIEMENS, Erlangen, Germany). All patients were instructed to fast for at least 4h, and patients analyzed from March 2016 to October 2017 received 100 mg of carbidopa 1 hr. prior to their examination. A CT scan was first recorded for each patient, immediately followed by a 30-min 3D list mode PET recording initiated during the bolus injection of 3 MBq of ^{18}F -FDOPA per kilogram of body weight. Static PET images were reconstructed from the list mode data acquired 10 to 30 min post-injection, while dynamic PET images consisted of 30 frames of one minute each [12]. Static and dynamic images were reconstructed using the OSEM 2D algorithm (2 iterations, 21 subsets, 4-mm Gaussian post-reconstruction filter, 256 x 256 x 148 voxels of 2.7 x 2.7 x 3.0 mm³). All images were corrected for attenuation using CT, dead time, random and scattered coincidences during the reconstruction process.

Image analyses

Segmentation, The LIFEx software (lifexsoft.org) was used to define volumes of interest (VOIs) for tumors and contralateral healthy brain [13].

A patient specific crescent shape VOI, which encompassed both white and grey matter, was manually drawn on the unaffected hemisphere to measure healthy brain uptake as recommended [14].

In tumors, VOIs were segmented semi-automatically using a threshold of 1.6 healthy brain SUV_{mean} [15]. For tumors with multiple loci, we only considered the site on which the neuropathological diagnosis was performed. All final VOIs were visually inspected by an experienced physician (A.V.) to ensure that the quality of the methods applied was consistent throughout.

Extraction of parameters, For static images, the SUV_{mean} , SUV_{max} , and SUV_{peak} parameters were extracted from the previously described VOIs for healthy brain and tumors.

For the radiomics analysis, 105 features were extracted from the same brain and tumor VOIs. These included morphological, local intensity, intensity-based statistical, intensity histogram and textural parameters. In accordance with the guidelines and benchmark values of the image standard biomarker initiative [16], 103 parameters were extracted using PyRadiomics and 2 local-intensity parameters, that were not available on PyRadiomics, were extracted with in-house software [12]. These radiomics parameters were extracted as detailed elsewhere [12]. Briefly, isotropic voxel resampling was performed using tricubic spline interpolations, before carrying out an absolute discretization of PET intensities with a fixed bin size of 0.1. Parameters were computed from a single matrix after merging all 3D directional matrices.

To potentially correct for any carbidopa premedication effects in our population, all static and radiomics parameters, except morphological features, in tumors were re-extracted after normalizing each static image for the SUV_{mean} 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 [17]. The SUV_{mean} values for each frame were respectively computed in the brain VOI and in the VOI corresponding to the tumor SUV_{peak} on the static image to extract the brain and tumor time activity curves (TACs). TACs were fitted to overcome noise effects [12]. As previously defined, two dynamic parameters were extracted: time-to-peak (TTP) and slope [18].

As for parameters extracted from static images, a normalized version of the parameters was extracted from a TAC representing the evolution of the ratio between tumor and brain fitted TACs to potentially correct for any carbidopa premedication effect [12].

Further analyses to confirm our hypotheses were performed on simulated data (methodology in Supplemental Materials and Supplemental Figure 1).

Statistical analysis. Categorical variables are expressed as percentages and continuous variables as medians and interquartile ranges. Intergroup comparisons were performed with the Chi-squared test for categorical variables and the Mann-Whitney test for continuous variables. Mann-Whitney tests were performed to compare carbidopa-naïve and premedicated patients in healthy brain VOIs. Correlations between radiomics features and SUV_{mean} were assessed using the Spearman correlation coefficient. Correction of multiples tests was performed with the Benjamini-Hochberg correction and $p < 0.05$ was considered significant. For tumor VOIs, linear regression analyses were performed to predict the parameters using carbidopa status and histo-molecular diagnosis as covariates, as histo-molecular diagnosis is known to influence static and dynamic parameters (gliomas were classified as IDH-wildtype and IDH-mutant astrocytomas, IDH-mutant and 1p/19q co-deleted oligodendrogliomas, and IDH-wildtype and IDH mutant glioblastomas) [18]. The significance of each covariate was tested using a type III analysis of variance. Analyses were performed with the R software version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria), and Python (Python Software Foundation).

Results

Patient characteristics

Fifty-four patients with a median age of 44 [19.8;82.6] years, comprised of 19 (35%) women, and 18 (33%) patients who were premedicated with 100mg of carbidopa, were included in the study. Dynamic acquisitions were available for 41 of these patients (median age of 45.2 [19.8;73.7] years, 14 (34%) women, and 11 (27%) patients had been premedicated with carbidopa). Detailed patient characteristics are provided in Table 1.

Carbidopa effects

Carbidopa induced an increase in all static and dynamic parameters in the brain, compared to patients that were not premedicated with carbidopa, with $\Delta SUV_{mean} = +53\%$, $\Delta TTP = +48\%$ and $\Delta slope = +88\%$ (all with $p < 0.001$) (Table 2). Furthermore, in healthy brain, 81% of radiomics features were impacted by carbidopa, 92% of these correlated with SUV_{mean} (absolute correlation coefficient ≥ 0.4) (Figure 1).

In tumors, carbidopa premedication was an independent predictor of SUV_{mean} ($\Delta SUV_{mean} = +52\%$, $p < 0.001$) and TTP ($\Delta TTP = +24\%$, $p = 0.025$). Histo-molecular diagnosis was predictive of TTP ($p = 0.010$) and slope ($p < 0.001$) and a trend was observed for the SUV_{mean} ($p = 0.07$). Interestingly, all static, dynamic and radiomics parameters were no longer significantly modified by carbidopa premedication when using tumor-to-healthy-brain image ratios or time-activity curve ratios (Table 3 and Supplementary Table).

To confirm our hypotheses about the impact of carbidopa premedication on TTP and better understand its effect on slope, simulated TACs were performed with carbidopa premedication on the assumption that carbidopa premedication induces an increase of radiotracer availability through the input function, i.e. the plasma concentration of ^{18}F -FDOPA, without modifying the rate constants.

Examples of simulated carbidopa premedication leading to increased TTP are displayed in Figure 2.

Discussion

This study shows that carbidopa premedication before ^{18}F -FDOPA PET imaging of brain tumors is associated with an increase in SUV, SUV-related radiomics and TTP dynamic parameters, of a global same order of magnitude as healthy brain. For neuro-oncological PET indications, the effect of the costly carbidopa premedication is thus limited by the use of TBR images and TAC ratios which are efficient tools for multicentric studies harmonization.

Carbidopa premedication in the present study increases the SUV_{mean} by about 50% in healthy brain tissue as well as and in brain tumors (Table 2 and 3). To the best of our knowledge only one previously published study has to date evaluated the effects of carbidopa in brain tumors, by comparing two patients with stable brain tumors, premedicated with 200mg of carbidopa at baseline and reevaluating these same patients without premedication one year later. Consistently with our study, this previous study also reported a 50% increased uptake in all brain structures, including healthy brain and tumors from acquisitions performed 15 to 25mn post-injection [9].

Our current study found that 81% of all radiomics parameters in healthy brain were significantly modified by carbidopa premedication, among which 92% correlated with SUV_{mean} (85 parameters, absolute correlation coefficient ≥ 0.4 in 78 parameters) (Figure 1). This underlines the fact that the effect of carbidopa premedication is related to a relatively homogeneous increase in the uptake of the ^{18}F -FDOPA radiotracer within the VOIs. The impact of SUV values on textural features has already been highlighted by Orhac et al. [19]. As we are using absolute discretization here, the increase in SUV related to carbidopa premedication induced two concomitant observations: i. a shift of textural matrices to higher bin values (bin shift) mainly responsible for the modification of the parameters correlated with the SUV values and, ii. a relative spread of the distribution of SUV values over a larger number of bins (bin spread). Eight percent of radiomics features (7 parameters, Supplemental Figure 2) were significantly modified by carbidopa premedication but poorly correlated with SUV_{mean} values (absolute correlation coefficients ranging from 0.27 to 0.34). Beyond the impact of a threshold effect, we presume that these parameters are less correlated with SUV_{mean} because they mainly depend on the bin spread effect, for which the impact on radiomics parameters is less directly correlated with SUV_{mean} than the bin shift effect. The bin spread effect on the involved matrices is illustrated in Supplemental Figure 2. Among the 20 remaining parameters, most are not significantly modified by carbidopa premedication since they are not correlated with SUV_{mean} values (Figure 1).

In our study, carbidopa also induced changes in the dynamic analysis parameters with an increase of TTP in healthy brain and in tumors. In tumors, this effect was independent of the histo-molecular diagnosis, which is known to affect the TTP of the dynamic analysis [18,20–22]. Even if the slope parameter was influenced by the histo-molecular diagnosis, no significant predictive value of carbidopa premedication was observed in tumors while carbidopa induced a significant increase of the slope in healthy brain. To confirm our findings in patients, we performed simulations on the assumption that carbidopa premedication leads to an increase in the plasma availability of ^{18}F -FDOPA without modifying the rate constants (Supplemental Materials). The two cases based on these simulations presented in Figure 2 confirm that the TTP increase was related to carbidopa premedication, similarly to what was observed in patients. Moreover, an increase of the slope was also observed in the simulated data. It is of concern that the TTP increase due to carbidopa premedication could potentially lead to an underestimation of tumor aggressiveness. In fact, this probability is moderate as regards the small degree of variation observed in the absolute values of TTP and slope in the tumors after simulation of carbidopa premedication (around +4 minutes and +0.5 SUV/h respectively).

Interestingly, when extracted from TBR images and TAC ratios, all static, dynamic and radiomics parameters were no longer significantly modified by the carbidopa premedication (Table 3 and Supplementary Table). This is an important observation, as TBRs are typically implemented in the routine analysis of neuro-oncology scans. These ratios were used in most articles in the literature for static [23,24], dynamic [18] and radiomics [12] parameters but without having been yet validated as to the effect of the carbidopa premedication.

Since glioma is a rare pathology, the need of multicentric studies to gather enough patients is even more important. These multicentric studies could be conducted only after performing harmonization between the participating centers. Regarding the carbidopa premedication, since its use is very dependent of each center, the harmonization process could come from the use of TBR images and TAC ratios, that have been shown to be insensitive to carbidopa premedication in this study, without modifying the protocols of participating centers. While, the ^{18}F -FDOPA PET guidelines for imaging of Parkinsonian syndromes [10] recommend carbidopa premedication to increase the systemic and thus central nervous system availability of ^{18}F -FDOPA. This recommendation is completely different in brain tumors, given that, unlike striatum, brain tumor cells do not metabolize ^{18}F -FDOPA [9]. This is presumably why recommendations for ^{18}F -FDOPA PET imaging do not include mandatory carbidopa premedication prior to brain tumor scans. This recommendation is however not founded on any evidence-based data from the literature and our study therefore provides additional information which supports the current recommendation.

Our retrospective study was performed on a heterogeneous population of patients, and therefore limits the ability to directly compare the effects of carbidopa premedication in tumors. Our hypotheses on the effects of carbidopa premedication were nevertheless confirmed by using simulated data. In our department, the patient carbidopa status was predicated by the recruitment period, this may have introduced an inclusion bias. However, no significant differences were observed between the two groups of patients (Table 1).

Conclusion

Our current study documents the effects of carbidopa premedication on the ^{18}F -FDOPA PET imaging of brain tumors. Carbidopa premedication leads to an increase in the availability of ^{18}F -FDOPA in plasma without modifying the rate constants. As carbidopa premedication increases the SUV, SUV-dependent radiomics and TTP dynamic parameters by a global same order of magnitude in healthy brain as in tumor, these effects are compensated for after taking into account the tumor-to-healthy-brain ratios in static images or in time-activity curves, which is an important point for multicentric studies harmonization.

References

1. Heiss W-D, Wienhard K, Wagner R, Lanfermann H, Thiel A, Herholtz K, et al. F-Dopa as an Amino Acid Tracer to Detect Brain Tumors. *J Nucl Med*. 1996;37:1180–2.
2. Albert NL, Weller M, Suchorska B, Galldiks N, Soffietti R, Kim MM, et al. Response Assessment in Neuro-Oncology working group and European Association for Neuro-Oncology recommendations for the clinical use of PET imaging in gliomas. *Neuro-Oncol*. 2016;18:1199–208.
3. Law I, Albert NL, Arbizu J, Boellaard R, Drzezga A, Galldiks N, et al. Joint EANM/EANO/RANO practice guidelines/SNMMI procedure standards for imaging of gliomas using PET with radiolabelled amino acids and [^{18}F]FDG: version 1.0. *Eur J Nucl Med Mol Imaging*. 2019;46:540–57.
4. Verger A, Kas A, Darcourt J, Chinot O, Taillandier L, Hoang Xuan K, et al. Joint SFMN/ANOCEF focus on ^{18}F -FDOPA PET imaging in glioma: Current applications and perspectives. *Médecine Nucl*. 2020;44:164–71.
5. Kobayashi K, Ohnishi A, Promsuk J, Shimizu S, Kanai Y, Shiokawa Y, et al. Enhanced Tumor Growth Elicited by L-Type Amino Acid Transporter 1 in Human Malignant Glioma Cells. *Neurosurgery*. 2008;62:493–504.
6. Papin-Michault C, Bonnetaud C, Dufour M, Almairac F, Coutts M, Patouraux S, et al. Study of LAT1 Expression in Brain Metastases: Towards a Better Understanding of the Results of Positron Emission Tomography Using Amino Acid Tracers. Debinski W, editor. *PLOS ONE*. 2016;11:e0157139.
7. Hoffman JM, Melega W, Hawk T, Grafton S. The Effect of Carbidopa Administration on 6-[^{18}F]Fluoro-L-DOPA Kinetics in Positron Emission Tomography. *J Nucl Med*. 1992;33:1472–7.
8. Huang S, Yu D, Grafton S, Melega WP, Hoffman JM. Kinetics and Modeling of L-6-esP]Fluoro-DOPA in Human Positron Emission Tomographic Studies. *J Cereb Blood Flow Metab*. 1991;11:898–913.
9. Schiepers C, Chen W, Cloughesy T, Dahlbom M, Huang S-C. ^{18}F -FDOPA Kinetics in Brain Tumors. *J Nucl Med*. 2007;48:1651–61.

10. Morbelli S, Esposito G, Arbizu J, Barthel H, Boellaard R, Bohnen NI, et al. EANM practice guideline/SNMMI procedure standard for dopaminergic imaging in Parkinsonian syndromes 1.0. *Eur J Nucl Med Mol Imaging*. 2020;47:1885–912.

11. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol (Berl)*. 2016;131:803–20.

12. Zaragori T, Oster J, Roch V, Hossu G, Chawki MB, Grignon R, et al. 18F-FDopa PET for the non-invasive prediction of glioma molecular parameters: a radiomics study. *J Nucl Med*.

13. Nioche C, Orlhac F, Boughdad S, Reuze S, Goya-Outi J, Robert C, et al. LIFEx: A Freeware for Radiomic Feature Calculation in Multimodality Imaging to Accelerate Advances in the Characterization of Tumor Heterogeneity. *Cancer Res*. 2018;78:4786–9.

14. Unterrainer M, Vettermann F, Brendel M, Holzgreve A, Lifschitz M, Zähringer M, et al. Towards standardization of 18F-FET PET imaging: do we need a consistent method of background activity assessment? *EJNMMI Res*. 2017;7:48.

15. Cicone F. The mean striatal 18F-DOPA uptake is not a reliable cut-off threshold for biological tumour volume definition of glioma. *Eur J Nucl Med Mol Imaging*. 2018;46:1051–3.

16. Zwanenburg A, Vallières M, Abdalah MA, Andrearczyk V, Apte A, Ashrafinia S, et al. The Image Biomarker Standardization Initiative: Radiology. 2020;00:1–11.

17. Ye H, Wong K-P, Wardak M, Dahlbom M, Kepe V, Barrio JR, et al. Automated Movement Correction for Dynamic PET/CT Images: Evaluation with Phantom and Patient Data. *PLOS ONE*. 2014;9:12.

18. Ginot M, Zaragori T, Marie P-Y, Roch V, Gauchotte G, Rech F, et al. Integration of dynamic parameters in the analysis of 18F-FDopa PET imaging improves the prediction of molecular features of gliomas. *Eur J Nucl Med Mol Imaging*. 2020;47:1381–90.

19. Orlhac F, Soussan M, Chouahnia K, Martinod E, Buvat I. 18F-FDG PET-Derived Textural Indices Reflect Tissue-Specific Uptake Pattern in Non-Small Cell Lung Cancer. *PLOS ONE*. 2015;10:16.

20. Verger A. Static and dynamic 18F-FET PET for the characterization of gliomas defined by IDH and 1p/19q status. *Eur J Nucl Med Mol Imaging*. 2018;45:443–51.

21. Vettermann F, Suchorska B, Unterrainer M, Nelwan D, Forbrig R, Ruf V, et al. Non-invasive prediction of IDH-wildtype genotype in gliomas using dynamic 18F-FET PET. *Eur J Nucl Med Mol Imaging*. 2019;46:2581–9.

22. Lohmann P, Herzog H, Rota Kops E, Stoffels G, Judov N, Filss C, et al. Dual-time-point O-(2-[18F]fluoroethyl)-L-tyrosine PET for grading of cerebral gliomas. *Eur Radiol*. 2015;25:3017–24.

23. Chen W, Silverman DHS, Delaloye S, Czernin J, Kamdar N, Pope W, et al. 18F-FDOPA PET Imaging of Brain Tumors: Comparison Study with 18F-FDG PET and Evaluation of Diagnostic Accuracy. *J Nucl Med*. 2006;47:904–11.

24. Janvier L, Olivier P, Blonski M, Morel O, Vignaud J-M, Karcher G, et al. Correlation of SUV-Derived Indices With Tumoral Aggressiveness of Gliomas in Static 18F-FDOPA PET: Use in Clinical Practice. *Clin Nucl Med*. 2015;40:e429–35.

Tables

Table 1. Patient characteristics.

	Without carbidopa Premedication	With carbidopa Premedication	All patients	p value
n				
Static	36	18	54	
Dynamic	30	11	41	
Age (years)				
Static <i>median [range]</i>	45.2 [24.6;82.6]	37.4 [19.8;72.7]	44.0 [19.8;82.6]	0.21
Dynamic <i>median [range]</i>	46.7 [24.6;73.7]	33.3 [19.8;72.8]	45.2 [19.8;73.7]	0.13
Female gender <i>n (%)</i>				
Static	11 (31%)	8 (44%)	19 (35%)	0.48
Dynamic	10 (33%)	4 (36%)	14 (34%)	1
Primary histopathological type <i>n (%)</i>				
Static				
IDH-mutant astrocytoma				
Anaplastic	13 (36%)	3 (17%)	16 (30%)	
Non-anaplastic	4	1	5	
IDH-wildtype astrocytoma	9	2	11	
Anaplastic	6 (17%)	1 (6%)	7 (13%)	
Non-anaplastic	3	1	4	0.21
IDH-mutant and 1p/19q co-deleted oligodendroglioma	3	0	3	
Anaplastic	9 (25%)	5 (28%)	14 (26%)	
Non-anaplastic	6	2	8	
IDH-wildtype glioblastoma	3	3	6	
IDH-mutant glioblastoma	6 (17%)	6 (33%)	12 (22%)	
	2 (6%)	3 (17%)	5 (9%)	
Dynamic				
IDH-mutant astrocytoma				
Anaplastic	13 (43%)	2 (18%)	15 (37%)	
Non-anaplastic	4	1	5	
IDH-wildtype astrocytoma	9	1	10	
Anaplastic	4 (13%)	0 (0%)	4 (10%)	0.17
Non-anaplastic	2	0	2	
IDH-mutant and 1p/19q co-deleted oligodendroglioma	2	0	2	
Anaplastic	7 (23%)	4 (36%)	11 (27%)	
Non-anaplastic	5	2	7	
IDH-wildtype glioblastoma	2	2	4	
IDH-mutant glioblastoma	5 (17%)	5 (45%)	10 (24%)	
	1 (3%)	0 (0%)	1 (2%)	

p-value for comparing patients with and without carbidopa premedication

Table 2. Healthy brain extracted parameters in patients without and with carbidopa premedication.

Parameter	Without carbidopa premedication	With carbidopa premedication	Correla- tion coeffi- cient with SUV _{mean}	p value	Mean relative difference in % (mean absolute difference) between patients without and with carbidopa premedication	Median relative difference in % (median absolute difference) between patients without and with carbidopa premedication
Static features (in-house software)						
SUV _{mean}	1,2 [1,02;1,32]	1,8 [1,53;2,08]	1	< 0,001	53,1% (+0,6)	46,4% (+0,5)
SUV _{max}	1,6 [1,45;1,75]	2,4 [2,03;2,68]	0,99	< 0,001	48% (+0,8)	41,3% (+0,7)
SUV _{peak}	1,4 [1,27;1,57]	2,1 [1,8;2,36]	0,99	< 0,001	50,2% (+0,7)	44,2% (+0,6)
Dynamic features (in-house software)						
TTP (min)	12,5 [10,74;13,64]	18,5 [17,03;18,96]	0,61	< 0,001	48,5% (+6,1)	46,2% (+5,6)
Slope (SUV/h)	-0,52 [-0,69;-0,39]	-0,06 [-0,18;0,01]	0,35	< 0,001	87,8% (+0,5)	70% (+0,4)

p-value for comparing patients without and with carbidopa premedication (in bold, significant p-values); absolute correlation coefficients ≥ 0.4 are in bold; TTP: time-to-peak; SUV: Standard Uptake Value

Table 3. Brain tumor extracted parameters in patients without and with carbidopa premedication and after normalization for healthy brain parameters with Tumor to normal Brain Ratios (TBR).

Parameters	Without carbidopa premedication	With carbidopa premedication	Corre-lation coefficient with SUV _{mean}	p value	Mean relative difference in % (mean absolute difference) between patients without and with carbidopa premedication	Median relative difference in % (median absolute difference) between patients without and with carbidopa premedication	TBR Without carbidopa premedication	TBR With carbidopa premedication	TBR p value
Static features (in-house software)									
SUV _{mean}	2,4 [1,94;2,8]	3,6 [3,14;4,06]	1	< 0,001	51,9% (+1,2)	48% (+1,1)	2,1 [1,78;2,19]	2,1 [1,87;2,15]	0,45
SUV _{max}	4,1 [2,6;5,15]	5,8 [4,08;7,18]	0,84	0,034	41,4% (+1,7)	41,9% (+1,5)	3,5 [2,18;4,26]	3,3 [2,44;4,09]	0,29
SUV _{peak}	3,4 [2,02;4,21]	4,9 [3,62;6,16]	0,86	0,034	44,1% (+1,5)	51,2% (+1,5)	2,9 [1,84;3,49]	2,8 [1,98;3,31]	0,33
Dynamic features							12,2 [2,83;23,15]	10,3 [2,48;18]	0,69
TTP (mn)	12,2 [7,37;15,53]	15,1 [9,43;19,31]	0,02	0,025	24,1% (+2,9)	30,3% (+3,1)	-1,1 [-1,59;0,41]	-1,7 [-1,9;-0,02]	0,50
Slope (SUV/h)	-2,71 [-3,14;-0,62]	-3,18 [-3,67;0,14]	-0,27	0,962	-17,6% (-0,5)	-93,8% (-1,1)	2,1 [1,78;2,19]	2,1 [1,87;2,15]	0,45

p-value for the predictive value of the carbidopa premedication in a linear regression model also including histo-molecular diagnosis without and with Tumor to normal Brain ratios (TBR) (in bold, significant p-values). Absolute correlation coefficients in bold are ≥ 0.4 . TTP: Time to Peak; SUV: Standardized Uptake Value

Figures

Figure 1

Effect of carbidopa premedication on healthy brain radiomics parameters.

Figure 2

Typical examples of patients without carbidopa premedication (C0) simulated with the effects of 100mg carbidopa premedication (C100). A. 18F-FDOPA PET time-activity curves expressed as SUV_{mean} (left panel) of a 59-year-old woman with IDH wildtype glioblastoma. Carbidopa induces a longer TTP (TTP C0 = 9mn. TTP C100 = 12.8mn) and an increase of the slope (slope C0 = - 4 SUV/h. SUV C100 = - 3.1 SUV/h). 18F-FDOPA PET time-activity curves expressed in TBR_{mean} (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. 18F-FDOPA PET time-activity curves expressed as SUV_{mean} (left panel) of a 65-year-old man with oligodendroglioma. Carbidopa induces a longer TTP (TTP C0 = 13.6 mn. TTP C100 = 17.2 mn) and an increase in the slope (slope C0 = -0.7 SUV/h. SUV C100 = -0.3 SUV/h). 18F-FDOPA PET time-activity curves expressed as TBR_{mean} (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 = 10.4 mn vs TTP C100 = 11 mn; slope C0 = -0.45 SUV/h vs slope C100 = -0.4 SUV/h)

Supplementary Files

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