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SHORT COMMUNICATION

Multiparametric evaluation of low grade gliomas at follow-up: comparison between diffusion and perfusion MR with ^{18}F-FDOPA PET

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Objective: To compare MRI using perfusion and diffusion techniques with 6-[^{18}F]-fluoro-L-3,4-dihydroxyphenylalanine (^{18}F-FDOPA) positron emission tomography (PET) in the follow-up of low-grade gliomas (LGGs) and to identify the best imaging parameter to differentiate patients with different prognosis.

Methods: Between 2010 and 2015, 12 patients with a pathology-proven diagnosis of LGG and MR (with perfusion and diffusion sequences) and a PET study during their follow-up were retrospectively included in our study. Cerebral blood volume (CBV) and apparent diffusion coefficient (ADC) maps on MR studies and PET images were evaluated using a region of interest-based method. All patients were categorized as stable or as having progressive disease at 1-year follow-up. Statistical analysis was performed using Pearson's correlation test and multivariate analysis of variance ($p < 0.05$).

Results: No significant correlations were found between PET parameters [maximum tumour-to-controlateral normal brain ratio (T/N_{max}) and tumour-to-striatum ratio] and ADC or relative CBV values measured in both PET hotspot regions and areas of maximum signal alterations. T/N_{max} demonstrated a good sensitivity (83%) and specificity (100%) for differentiating two subgroups of patients with different outcomes at 1-year-follow-up ($p < 0.05$).

Conclusion: Perfusion and diffusion MR images provide different information compared with ^{18}F-FDOPA PET in LGGs during follow-up and therefore, they should be considered as complementary tools in the evaluation of these tumours. ^{18}F-FDOPA PET showed a significant prognostic role in the follow-up of LGGs and appeared to be a better tool than MR advanced techniques for outcome prediction. These results need to be confirmed with longitudinal studies on a larger population.

Advances in knowledge: This is the first study that compared ^{18}F-FDOPA PET with perfusion and diffusion MR in LGGs during follow-up. These preliminary results highlight the importance of a multimodality approach in this field and evidence a potential role for ^{18}F-FDOPA PET to predict patients at risk for tumour progression.

INTRODUCTION

Supratentorial World Health Organization (WHO) grade II gliomas, also called low-grade gliomas (LGGs), represent a group of extremely heterogeneous tumours for pathologic, clinical and molecular features classified as astrocytomas, oligodendrogliomas and oligoastrocytomas.[1]

The natural history of these lesions is constant disease progression towards malignant transformation, with different times and percentages according to histology.[2] The main imaging challenges at diagnosis and follow-up consist of correct tumour grading, delineation of disease volume and prognosis definition. This is especially important because so far, there is no clear consensus on the correct therapeutic management and a holistic knowledge of the tumour on an individual-based approach has been suggested.[1,3] Early surgical complete resection is recommended for patients with operable tumours, whereas different strategies should be evaluated in patients with inoperable lesions, adopting a constant clinical and imaging surveillance to identify early imaging signs of tumour aggressiveness before malignant transformation.[4] The same is true for residual tumour after surgery.

So far, the utility of advanced imaging techniques has not been fully understood, especially in the follow-up of LGGs. To date, perfusion imaging with dynamic susceptibility contrast (DSC) MRI has been proposed as a useful tool in glioma follow-up, suggesting a high sensitivity and specificity for relative cerebral blood volume (rCBV) values to predict survival and malignant transformation, respectively, also compared with conventional MRI sequences.[5,6]

In the past decade, nuclear medicine has obtained an increasing attention in glioma imaging, especially demonstrating the utility of amino acid radiotracers in managing these tumours. Among different amino acids, the most widely used is ^{11}C-methionine, which has been shown to have a high sensitivity and specificity in detecting LGGs, but has a short half-life, limiting its use to centres endowed with a cyclotron. On the other hand, 6-[^{18}F]-fluoro-L-3,4-dihydroxyphenylalanine (^{18}F-FDOPA) has a longer half-life (110 min) and therefore may represent a good alternative, providing a similar sensitivity in tumour detection.[7] Different studies have also shown a potential role of ^{18}F-FDOPA positron emission tomography (PET) in predicting survival in patients affected by gliomas, but so far its correlation with advanced MR sequences such as DSC and diffusion-weighted imaging (DWI) during the follow-up of LGGs has not been investigated yet.[8]

The purpose of this retrospective study was to explore the correlations between DSC, DWI-derived maps and ^{18}F-FDOPA PET in LGGs during follow-up and to identify the best imaging parameter to differentiate patients with different prognosis.

METHODS AND MATERIALS

Patient characteristics and follow-up

All patients with pathology-proven LGG with MR scans acquired between January 2012 and December 2015 at Sant'Andrea University (Sapienza) Hospital of Rome were reviewed.

Patients were included in this retrospective analysis if they fulfilled the following criteria: (a) pathology-proven LGG; (b) at least one MR examination during follow-up with DSC and DWI sequences; demonstrating an area of T_2 signal hyperintensity on fluid-attenuated inversion-recovery (FLAIR) images; (c) an ^{18}F-FDOPA PET performed within 6 weeks from the MR study selected; and (d) 1-year MR and clinical follow-up after the selected MR-PET studies. Exclusion criteria were: (1) the presence of radiological signs of malignant transformation at the initial MR examination selected (appearance of a new area of enhancement on post-contrast T_1 weighted sequences).

Our local ethics committee approved this study.

MR acquisition

All MR scans were performed on a 1.5-T unit (Siemens Sonata, Erlangen, Germany) equipped with a four-channel phased-array head coil. MR standard brain protocol included axial spin-echo T_1 weighted, T_2 weighted, FLAIR and DWI sequences. Diffusion-weighted images were acquired in three orthogonal planes with three levels of diffusion sensitization (b-values 0, 500 and 1000 s mm^{-2}) and the following parameters: section thickness, 5 mm; repetition time (TR), 3000 ms; echo time (TE), 84 ms; intersection gap, 0.3 mm; matrix, 256 × 256 mm; and acquisition time, 1.40 min. DSC images were obtained with a T_2* weighted gradient-echo echoplanar imaging sequence [TR/TE 1490/40 ms, flip angle 90°, field of view (FOV) 230 × 230 mm, matrix 128 × 128, 14 sections of thickness 5 mm and acquisition time 78 s] during bolus injection of gadopentetate dimeglumine (Dotarem®; Guerbet, Villepinte, France) (dose 0.1-mmol kg^{-1} body weight, injection rate 4 ml s^{-1}), followed by a 20-ml saline flush. T_1 weighted three-dimensional magnetization-prepared rapid acquisition gradient-echo images (TR/TE 1840/4.4 ms, section thickness 1 mm, inversion time 110 ms, FOV 188 × 250 mm, matrix 238 × 256) were acquired after the DSC sequence.

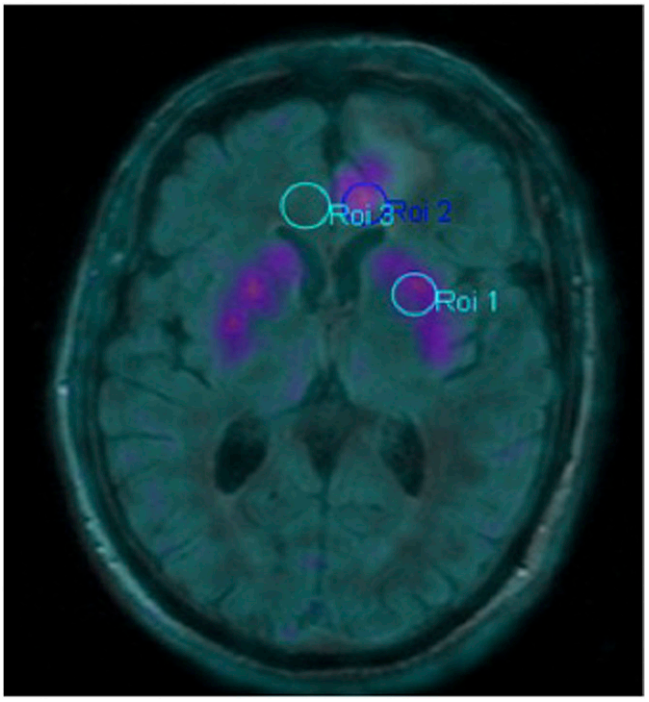
DSC-MR data were transferred to a Siemens Leonardo workstation (Siemens Medical Solutions, Siemens, Erlangen, Germany) and retrospectively processed by two experienced readers in consensus (AR and MCRE). In order to calculate rCBV maps, we used the semi-automated arterial input function method derived from a region of interest (ROI) located close to the middle cerebral artery contralateral to the lesion side.

Positron emission tomography acquisition

One 20-min static image of the brain was acquired on a Philips Gemini PET/CT camera (Philips Medical Systems, the Netherlands) starting 15 ± 5 min after the i.v. injection of 185 MBq (range 148–196 MBq) of ^{18}F-FDOPA.

Patients were required to fast for at least 6 h before the scan and no carbidopa premedication was given. A low-dose,

Figure 1. Positron emission tomography (PET)-based method: in order to obtain tumour-to-normal brain and tumour-to-striatum ratios, regions of interest (ROIs) were drawn on co-registered axial MR fluid-attenuated inversion-recovery and PET images in tumoral hotspot area (ROI2), contralateral brain region (ROI3) and homolateral striatum (ROI1). ROIs in hotspot regions were then copied on relative cerebral blood volume and apparent diffusion coefficient maps.



non-contrast-enhanced CT scan (120 kV, 60 mA) was acquired for attenuation correction. Images were reconstructed using a three-dimensional row-action maximization-likelihood algorithm (RAMLA) on a 128 × 128 matrix and a square FOV of 256-mm side, yielding a final voxel of 8 mm^3.

Positron emission tomography analysis

For the correct identification of brain lesions, PET/CT images, rCBV and apparent diffusion coefficient (ADC) maps were fused together with FLAIR sequences on a Hermes workstation (Hermes Medical Solutions, Stockholm, Sweden) using a semi-automatic registration tool. If necessary, registration was manually adjusted on all the three axes.

On PET scans, a circular ROI of 50 mm^2 was drawn around the lesion on the brain slice containing the five hottest pixels of the lesion (hotspot) (Figure 1). Maximum lesion and basal ganglia uptake values were recorded. The basal ganglia were always visible on PET images owing to the physiological uptake mechanism of F-FDOPA.[9]

Reference ROIs were also drawn on the normal-appearing contralateral side for background uptake. From these ROIs, the standardized uptake value (SUV) was calculated using the standard body weight method.

Obtained PET parameters were: maximum SUV, maximum tumour-to-contralateral normal brain (T/N_{max}) and maximum tumour-to-striatum ratio.

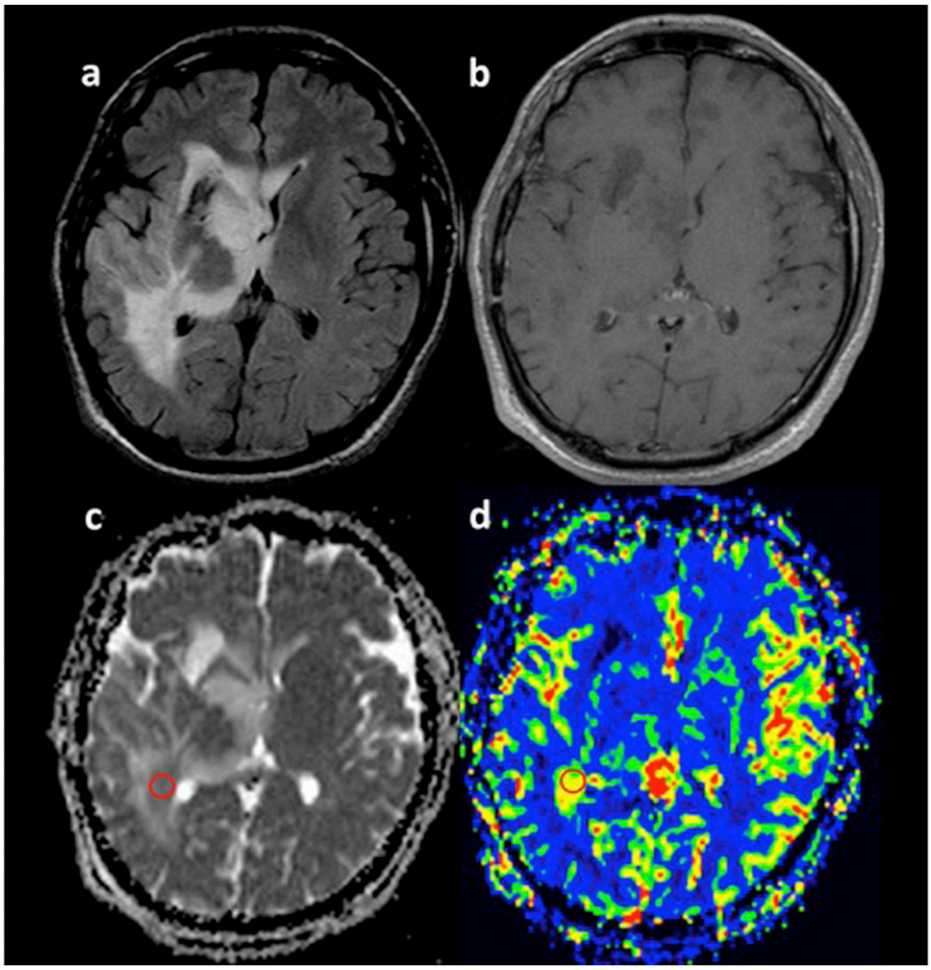
MR analysis

Two different methods were used to obtain perfusion and diffusion parameters as previously shown.[4]

First, from PET images, ROIs of the same size were copied on rCBV and ADC maps in order to obtain the maximum rCBV and minimum ADC in the hotspot region.

Secondly, perfusion and diffusion parameters were obtained independently from PET images. An ROI of 50 mm^2 was drawn on

Figure 2. MR based method: follow-up axial fluid-attenuated inversion-recovery images (a) demonstrating a diffuse area of signal hyperintensity in the right temporal lobe, right thalamus and basal ganglia regions with involvement on right periventricular white matter. The lesion is not showing contrast enhancement (b) and is consistent with recurrent diffuse low-grade glioma. In order to obtain values of minimum apparent diffusion coefficient (ADC) and maximum relative cerebral blood volume ($rCBV_{max}$), independently from positron emission tomography images, regions of interest were drawn on regions of low ADC values on ADC maps (c) (circle) and high rCBV values on rCBV maps (d) (circle). Both values were compared with contralateral normal-appearing white matter as reference and normalized minimum ADC values and $rCBV_{max}$ values were calculated.



regions showing maximum signal alterations to obtain maximum rCBV and minimum ADC values within the lesions (Figure 2).

On rCBV maps, all ROIs were drawn avoiding the blood vessels, cyst, necrosis and susceptibility artefacts.

All perfusion and diffusion parameters were normalized to mean rCBV and ADC values on contralateral normal-appearing white matter.

If no signal alterations could be appreciated on rCBV or ADC maps, ROIs were drawn on regions showing maximum signal alterations on FLAIR images (Figure 3).

STATISTICS

Pearson's correlation test was run to test the relationship between PET and MR measurements. Furthermore, to test the predictive factor of our variables, a multivariate analysis of variance with a model including the intercept, follow-up status variable and histology as covariates of no interest was performed. Receiver-operating characteristic analysis was performed to obtain the sensitivity and specificity for the variable reaching statistical significance.

The Statistical Package for the Social Sciences®, v. 20 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL) was used for statistical analysis.

RESULTS

Patient characteristics and follow-up

44 patients with pathology-proven LGG with MR scans acquired between January 2012 and December 2015 at Sant'Andrea University Hospital of Rome were reviewed. 25 patients were excluded because ^{18}F-FDOPA PET study was not acquired during follow-up; 7 patients were excluded because ^{18}F-FDOPA PET study was acquired after malignant transformation.

A total of 12 patients fulfilling the inclusion criteria were included for retrospective analysis.

FLAIR and contrast-enhanced T_1 weighted sequences on 1-year follow-up MR scans were considered to assess response to treatment, according to Response Assessment in Neuro-Oncology (RANO) criteria for LGGs.[10]

A total of 12 patients (5 males, 7 females) with a mean age of 51.4 years (range 34–78 years) affected by WHO grade II glioma were retrospectively enrolled.

Tumour diagnosis consisted of eight grade II oligodendrogliomas and four grade II astrocytomas.

Clinical and radiological follow-up was performed for 1 year after PET-MR examinations and disease status was assessed according to RANO criteria for LGGs.[10]

Patient and tumour characteristics are summarized in Table 1.

Correlation between positron emission tomography and MR parameters

In hotspot regions, mean T/N_{max} values were 1.8 [standard deviation (SD) $\pm$ 0.86] and mean maximum tumour-to-striatum ratio values were 0.93 (SD $\pm$ 0.44). Using the ^{18}F-FDOPA PET-guided approach, mean rCBV values in hotspot regions were 0.75 (SD $\pm$ 0.2), while mean normalized minimum ADC (nADC) values in the same regions were 0.97 (SD $\pm$ 0.17). There was no

Figure 3. Chart showing mean values of the evaluated positron emission tomography and MR parameters in two subgroups of patients with stable or progressive disease at 1-year follow-up. Maximum tumour-to-controlateral normal brain ratio (T/N_{max}) was the only value that showed a significant difference between the two groups on multivariate analysis of variance ($p < 0.05$). $nADC_{min}$ HS: minimum normalized apparent diffusion coefficient (ADC) in the hotspot region (HS); $nADC_{min}$ MR: minimum normalized apparent diffusion coefficient on magnetic resonance (MR); $rCBV_{max}$, maximum relative cerebral blood volume; $rCBV_{max}$ HS: maximum relative cerebral blood volume in the hotspot region (HS); $rCBV_{max}$ MR: maximum relative cerebral blood volume on magnetic resonance (MR); SUV_{max}, maximum standardized uptake value; T/S_{max}, maximum tumour-to-striatum.

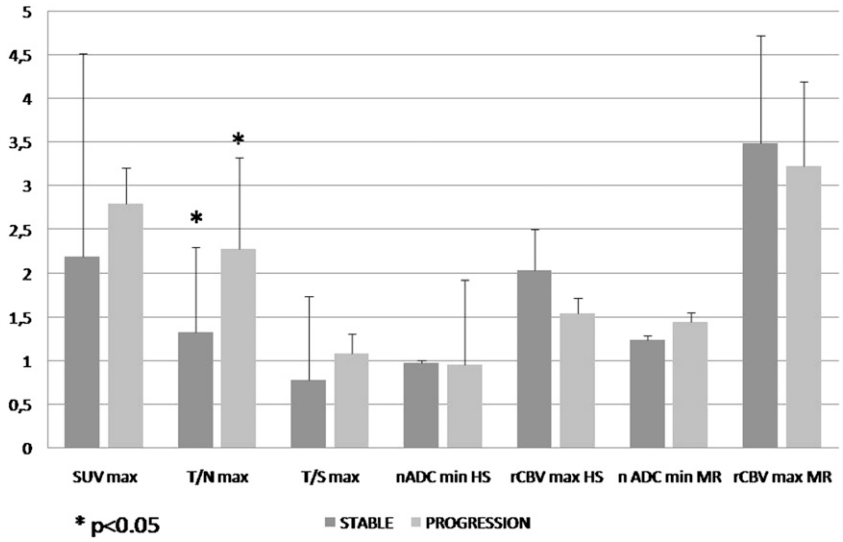


Table 1. Summary of patient demographic and clinical characteristics

Demographics and clinical features	Patients (n = 12)
Gender	
Male	5
Female	7
Age (years)	
Mean	51.4
Range	34–78
Histology	
Astrocytoma	4
Oligodendroglioma	8
Tumour location	
Left frontal lobe	6
Right frontal lobe	2
Left parietal lobe	1
Right parietal lobe	2
Left temporal lobe	1
Right temporal lobe	2
Eloquent regions	7
Non-eloquent regions	5
Treatment at diagnosis	
Complete resection	5
Subtotal resection	6
Biopsy	1
1-year follow-up (RANO criteria)	
Progression	6
Stable disease	6

correlation between ^{18}F-FDOPA PET uptake and nADC or rCBV values measured in hotspot areas.

Using the MR-guided approach, mean rCBV values were 1.89 (SD ± 1.78) and mean nADC values were 1.34 (SD ± 0.22). No statistical correlation was found between these values and ^{18}F-FDOPA PET uptake.

Analysis of variance and receiver-operating characteristic analysis

Multivariate analysis of variance demonstrated a significant correlation between follow-up status (stable *vs* disease progression) and T/N_{max} ($p < 0.05$). Receiver-operating characteristic analysis demonstrated a cut-off value of 1.7 with a sensitivity of 83% and a specificity of 100%.

Mean values for each evaluated parameter in each group (stable *vs* progression) are summarized in Figure 4.

DISCUSSION

As recently proposed by Duffau et al,[1] advances in genetics, imaging and treatments have revolutionized the knowledge of LGGs, suggesting to abandon a "wait and see" approach and start considering these lesions as a "*chronic disease of the Central Nervous System*" which may lead to progressive disability and cognitive decline until death. Therefore, multiple efforts have been demonstrated by several studies to explore different imaging modalities in order to provide useful information on disease progression and prognosis, with the ultimate purpose of identifying "early signs of anaplastic transformation" to arrange an appropriate and personalized treatment.

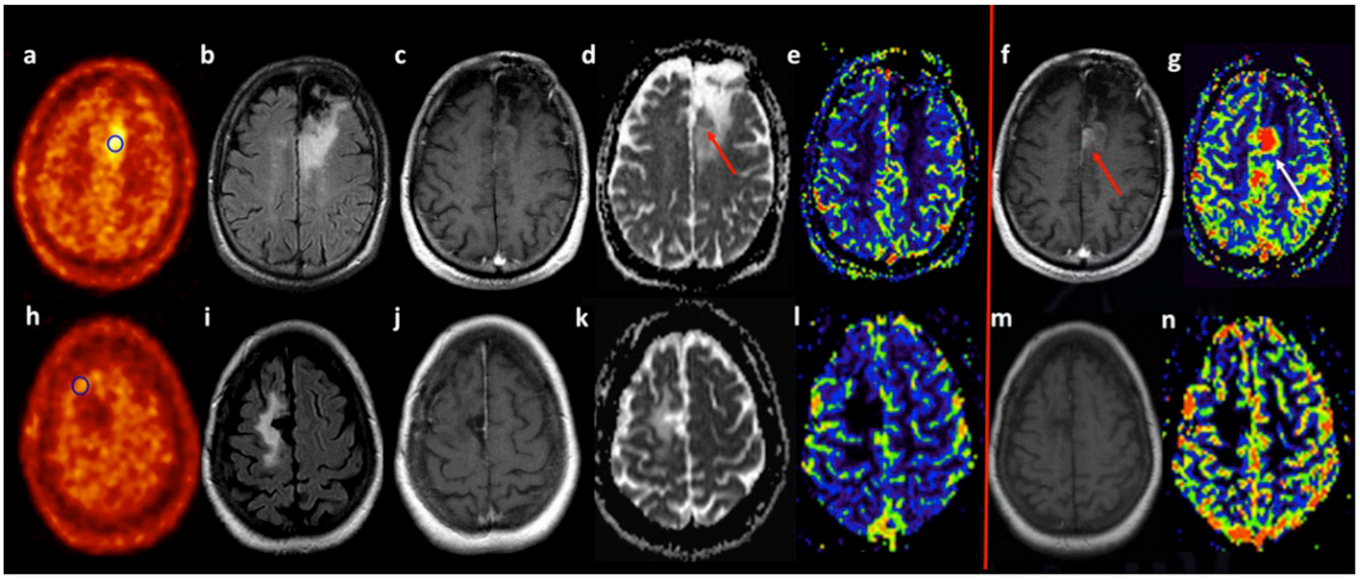
So far, response assessment criteria in gliomas have been based on conventional imaging (contrast-enhanced T_1 and T_2 weighted sequences), but in the past few years, they appeared to be inadequate to represent the biological activity of the tumour. Therefore, different advanced techniques such as perfusion, diffusion and spectroscopy MR sequences and amino acid PET have been widely explored in order to investigate the relationship between imaging and tumoral behaviour at diagnosis or at follow-up in order to correlate patient outcome with imaging features within the lesion.[11]

^{18}F-FDOPA PET has been widely explored in imaging gliomas, demonstrating the advantage of a longer half-life than the more used amino acid radiotracer ^{11}C-methionine, but having a similar tumour uptake, with a good sensitivity (ranging from 85 to 100%) and specificity (ranging from 89 to 100%).[12] However, only few studies have focused on its role in imaging LGGs on follow-up.[7]

This is the first study that compared advanced MR techniques such as perfusion and diffusion with ^{18}F-FDOPA PET in LGGs during follow-up. Our results demonstrated a lack of correlation between rCBV values and ^{18}F-FDOPA uptake, confirming the results of Cicone et al[13] in a larger cohort of patients including both LGGs and high-grade gliomas at recurrence or progression. No correlations were found while also comparing PET-derived parameters and nADC values obtained in both hotspot regions using a MR-guided approach. These results are in line with those shown by Rahm et al,[14] who compared the uptake of the amino acid O-(2-^{18}F-fluorethyl)-L-tyrosine with ADC values in the pre-operative evaluation of recurrent or progressive LGG. The lack of correlation between the two parameters may be explained by considering ADC values as not only the result of tumour cell density as often postulated, but as a more complex indicator of different tissue properties such as normal cell density, extracellular space volume, microvessels and the presence of macromolecules.[14]

We found that T/N_{max} ratio was the best parameter to distinguish two subgroups of patients with different prognoses at 1-year follow-up (progression *vs* stable disease) using RANO criteria for LGGs. Using a cut-off of 1.7, we obtained a sensitivity of 83% and a specificity of 100%. Similar results have been shown in a recent study by Villani et al,[8] who investigated the role of ^{18}F-FDOPA PET in a population of 50 patients with WHO grade II and III gliomas. The authors demonstrated that a maximum SUV of >1.75, together with disease duration, is an independent predictor of disease progression, regardless of clinical and conventional MR features.

Figure 4. Correlation between tumour-to-normal brain (T/N) ratio 6-[^{18}F]-fluoro-L-3,4-dihydroxyphenylalanine (^{18}F-FDOPA) positron emission tomography (PET) uptake and outcome: the top row is showing a case of a left frontal low-grade glioma (LGG) with ^{18}F-FDOPA PET images (a) during follow-up, demonstrating a high T/N ratio of 2.5 in the hotspot region (circle). A close MR examination is demonstrating a fluid-attenuated inversion-recovery (FLAIR) hyperintense lesion (b), without contrast enhancement (c) and with a small area of hypointensity on apparent diffusion coefficient (ADC) maps (d) (arrow), without increase in the relative cerebral blood volume (rCBV) values on CBV maps (e). Follow-up MR scan 1 year later is demonstrating the presence of a focus of enhancement (f) (arrow) and high rCBV values within the lesion (g) (arrow) consistent with disease progression. The bottom row is showing a companion case of a right frontal LGG with low values of T/N ratio (1.2) at ^{18}F-FDOPA PET images (h) (circle). Close MR scan demonstrated an area of FLAIR hyperintensity (i) without contrast enhancement (j) or evidence of decreased ADC (k) or increased rCBV values (l). Follow-up MR scan 1 year later is demonstrating unmodified radiologic findings on post-contrast T_1 weighted images (m) and rCBV maps (n), suggesting stable disease.



Based on our preliminary results, ^{18}F-FDOPA PET-derived parameter outperformed advanced MR techniques also, such as perfusion and diffusion, in distinguishing progressive *vs* stable disease in the follow-up of WHO grade II gliomas.

The present study, however, has different limitations. The sample size is small, thus reducing the power of the study. Moreover, among the different LGGs evaluated, there was a majority of oligodendrogliomas which, as already described in literature, may show increased amino acid uptake and high rCBV values that are not related to tumour grade but more consistently related to the co-deletion of chromosome 1p and 19q (1p/19q co-deletion), which was not investigated in all our patients.[15] However, in order to exclude this potential confounding factor from statistical analysis, in the multivariate analysis, histology was considered as a covariate of no interest. Finally, the maximum gap between MR and PET studies was 12 weeks, which may account for possible differences in the disease status; but, considering the slow-growing behaviour of these lesions, we hypothesize that it should not affect the comparison made.

For these reasons, any inference derived from these preliminary results should be confirmed by longitudinal and perspective analysis on a larger population.

CONCLUSION

In the follow-up of low grade gliomas, MRI with perfusion and diffusion techniques does not correlate with ^{18}F-FDOPA PET, thus providing different information. Therefore, in the follow-up of WHO grade II gliomas, they should be considered as complementary tools using a multimodality approach.

Compared with the advanced MR techniques, ^{18}F-FDOPA PET seems to have a better prognostic rule in the follow-up of LGG and further longitudinal studies on a larger population are necessary to validate these data also comparing ^{18}F-FDOPA uptake with molecular markers.

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