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## **Is IDH mutation status associated with 18F-FDopa PET uptake?**

Timothée ZARAGORI<sup>1,2</sup>, Eric GUEDJ<sup>3,4,5</sup>, Antoine VERGER<sup>1,2</sup>

<sup>1</sup>CHRU-Nancy, Université de Lorraine, Department of Nuclear Medicine & Nancyclotep  
Imaging platform, F-54000, Nancy, France

<sup>2</sup>Université de Lorraine, IADI, INSERM, UMR 1254, F-54000, Nancy, France

<sup>3</sup>Department of Nuclear Medicine, Assistance Publique-Hôpitaux de Marseille, Aix-Marseille  
Université, Timone University Hospital, Marseille, France

<sup>4</sup>CERIMED, Aix-Marseille Université, Marseille, France

<sup>5</sup> Aix-Marseille Université, CNRS, Ecole Centrale de Marseille, UMR 7249, Institut Fresnel,  
Marseille, France

Dear Sir, We read with great interest the recent article by Cicone et al. published in the Annals of Nuclear Medicine [1]. The authors state that 6-[18F]fluoro-L-DOPA (18F-FDopa) PET uptake is not significantly different between IDH-mutant and IDH-wildtype gliomas in a population composed of diffuse gliomas as well as glioblastomas. At first glance, these results appear to be inconsistent with regard to the article published earlier by our team [2]. Indeed, we concluded that the IDH mutation, which is a factor of good prognosis, was paradoxically associated with a higher uptake of 18F-FDopa PET in a series of diffuse gliomas. It is of particular interest to underline the potential of 18F-FDopa PET in brain tumors since this amino acid PET radiotracer has currently been recommended by joint EANM/EANO/RANO practice guidelines/SNMMI procedure standards for assessing gliomas at initial diagnosis [3]. In this perspective, we would like to propose our hypothesis on these apparently conflicting results and why they should be considered as two sides of the same effect as opposed to being contradictory. For this purpose, we have conducted new analyses to study the relationship between IDH mutation status and 18F-FDopa PET tumor uptake in a third distinct population of 58 gliomas derived from our recent publication [4]. The mean tumor-to-background ratio (TBR<sub>mean</sub>) and the metabolic tumor volume (MTV) were recalculated from a tumor VOI segmented by a threshold value of 1.6 of the healthy brain ROI. In case of non-detectable MTV, the TBR<sub>mean</sub> was calculated relative to a defined volume based on FLAIR images. This was applied in order to be the closest possible to the methodology utilized by Cicone et al. in their publication so as to avoid any methodological bias when comparing the two different populations. In addition, this VOI definition is in accordance with that recently proposed by the same group in response to the European/American guidelines [1, 5]. When considering our whole population including both diffuse gliomas and glioblastomas, we found that static parameters failed to differentiate IDH-mutant from IDH-wildtype gliomas ( $p=0.69$  for the TBR<sub>mean</sub> and  $p=0.53$  for MTV). However, when focusing the analysis on diffuse gliomas only, static parameters showed to be paradoxically associated with IDH mutation status, confirming the results of our previous article [2]. Specifically, the MTV was significantly higher in IDH-mutant diffuse gliomas ( $p=0.002$ ) while a substantial trend toward a higher TBR<sub>mean</sub> in these IDH-mutant diffuse gliomas was

also observed ( $p=0.10$ ). We then recalculated the data from Cicone et al.'s cohort [1]. Unfortunately, after excluding glioblastomas, although the mean MTV was higher in IDH-mutant than in IDH-wildtype diffuse gliomas (19.4 mL vs. 10.4 mL), this observation was not statistically significant. In our opinion, two main reasons can explain these results. Firstly, Cicone et al. did not use a fixed threshold to segment their tumor volume, leading to MTVs which were hardly comparable. Secondly, in the publication by Cicone et al., most patients underwent their stereotaxic biopsy prior to having undergone their  $^{18}\text{F}$ -FDopa PET, which can affect tumor uptake by removing a portion of the tumor (94% in [1] vs. 2% in [2] and 12% in [4]).

In summary, IDH mutation status is associated with  $^{18}\text{F}$ -FDopa PET tumor uptake in diffuse gliomas. This finding has been observed in two different studied populations [2, 4]. By contrast, as stated by Cicone et al., this relationship cannot be extended to a population including both diffuse gliomas and glioblastomas [1]. Predicting the IDH mutation status in the subgroup of diffuse gliomas is particularly useful from a clinical standpoint since glioblastomas can often be identified owing to contrast enhancement on contrast-enhanced T1-weighted MRI. It should nevertheless be added that, at initial diagnosis, dynamic parameters, studied in [4], are able to discriminate IDH-mutant from IDH-wildtype gliomas in both population types ( $p$

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