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LETTER TO THE EDITOR

The mean striatal ^{18}F-DOPA uptake is not a reliable cut-off threshold for biological tumour volume definition of glioma

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Dear Editor,

We were extremely interested in the procedural guidelines for imaging gliomas with amino acid and fluorodeoxyglocose PET, published jointly by the EANM/RANO/EANO and SNMMI in your journal [1]. Imaging with radiolabelled PET probes, particularly amino acids, has become an essential part of primary brain tumour assessment [2], and these joint guidelines represent an important step towards international standardization of the acquisition and interpretation criteria of this technique.

There is, however, one ambiguous point in these guidelines that needs to be addressed. This point regards the quantification of tumour extent with 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (FDOPA). In the paragraph "Cut-off thresholds for definition of biological tumour volume", a standardized uptake value (SUV) higher than the mean SUV of the striatum is recommended as the cut-off value for definition of tumour volume on FDOPA PET, although it is acknowledged that this cut-off value lacks histological validation [1]. This claim is supported by citation of an article written by a renowned American group, which used a tumour-to-striatum (T/S) cut-off ratio greater than 1 to study tumour volume changes in high-grade glioma during antiangiogenic therapy [3]. The same paper [3] is used elsewhere in the guidelines as the only reference on which to base the statements that: "The striatum is the most commonly used reference region. Other reference regions have not been investigated systematically" [1].

First, brain tumours, particularly low-grade tumours, showing FDOPA uptake lower than that of the basal ganglia are seen quite often in clinical routine (Fig. 1). For example, in a recent study by our group [4], 13 of 33 included patients (39%) had a mean tumour-to-basal ganglia uptake ratio less than 1. It is interesting to note that, in a previous study based on a cohort of 81 patients with glioma, the above-mentioned American group found that a T/S ratio >0.75 had better accuracy than a T/S ratio >1 (95% vs. 93%, respectively) [5]. Consequently, the use of a cut-off ratio with the worst performance as a reference is not justified.

Second, the statement that "Other reference regions have not been investigated systematically" does not take into account at least two biopsy-controlled studies that used tumour-to-normal brain ratio instead of T/S for definition of tumour extent [6, 7]. Several additional studies used tumour-to-normal contralateral brain ratio alone or in combination with T/S ratio for definition of tumour extent, albeit without systematic histological confirmation [4, 8–14].

Therefore, in our opinion, the recommendation to use the mean basal ganglia uptake as the sole reference standard for definition of tumour volume is not evidence-based and could be misleading. If the recommendation was taken

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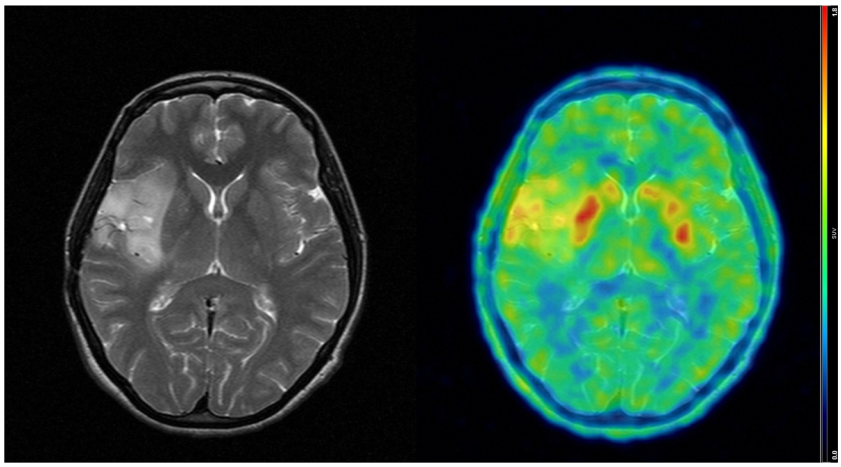

Fig. 1 Magnetic resonance and FDOPA axial imaging of a non contrast-enhancing, biopsy-proven right frontotemporal grade II oligodendroglioma according to the WHO 2016 classification. The FDOPA tumour uptake is clearly lower than the physiological uptake in the striatum

literally, some centres might assign a low probability of malignancy to tumour portions showing FDOPA uptake lower than that of the striatum, thereby potentially generating false-negative reports.

Let us make a final remark. As suggested by recent studies of both FDOPA and FET, the uptake in normal-appearing brain structures, such as the contralateral brain parenchyma or the striatum, can be altered by temozolomide and dexamethasone, that are commonly used drugs in the workup of patients with glioma [14, 15]. These pharmacological interferences might also be relevant for tumour delineation, particularly when the biological tumour volume is defined relative to one of these normal-appearing brain structures. In view of this, we believe that a careful pharmacological anamnesis of past and ongoing treatments is of paramount importance for amino acid PET interpretation. This issue, however, is not sufficiently emphasized in the guidelines [1].

In summary, many brain tumours are less FDOPA-avid than the striatum; therefore, in our opinion, the mean uptake in the striatum should not be recommended as a cut-off value for definition of biological tumour volume. Potential effects of past or concurrent treatments should be carefully evaluated when the uptake in any normal-appearing brain structure is taken as reference for definition of tumour volume.

Compliance with ethical standards

Conflicts of interest None.

Ethical approval This article does not describe any studies with human participants or animals performed by any of the authors.

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