LETTER TO THE EDITOR

Response to “Reply to [18F]-fluoro-ethyl-L-tyrosine PET: a valuable diagnostic tool in neuro-oncology, but not all that glitters is glioma” by Hutterer et al.

Dear Editor,

We would like to thank Dr. Langen and Dr. Galldiks for their comments on our article¹ and take this opportunity to respond to the 3 major points discussed by the authors.

The first issue addresses the methodological approach of whether a brain lesion should be judged as [¹⁸F]-FET positive or negative on the basis of visual image interpretation or of the implementation of defined lesion-to-brain ratio (LBR) thresholds. With use of the visual approach, a brain lesion is considered to be positive if the [¹⁸F]-FET uptake in an MR-defined region of interest (ROI) is visually higher than the background activity in the corresponding contralateral hemisphere including white and grey matter. Alternatively, Drs. Langen and Galldiks recommend the use of a threshold-based approach to define a brain lesion being [¹⁸F]-FET PET positive or negative. According to a study from their group,² an LBR threshold > 1.6 best separated tumors from unspecific amino acid uptake. Of importance, this study was performed in a homogeneous cohort of 28 patients with gliomas. Such a standard LBR cutoff value, however, has never been validated for a heterogeneous patient population and was not feasible in our retrospectively evaluated cohort of 393 patients covering a broad variety of brain lesions, including primary glial and nonglial brain tumors of all malignancy grades and several nonneoplastic neurologic diseases. Similar approaches using visual PET image analysis have already been successfully implemented by other groups.³⁻⁵

In addition, several other approaches defining an [¹⁸F]-FET-positive lesion were published by using standard uptake values (SUVs) within a 90% or 40% isocontour,⁶,⁷ an automatic threshold-based region-growing algorithm,⁸ or by measuring the [¹⁸F]-FET uptake that was at least 110% of the cerebellar activity, which corresponded well to the visual impression of an active low-grade glioma.⁹

The guidelines of the European Association of Nuclear Medicine (EANM)¹⁵ for brain tumor imaging using labeled amino acid analogues recommend visual and quantification interpretation criteria, in which “quantification is helpful in assisting visual interpretation and to objectivize tumor uptake of labeled amino acids” but not considered to be mandatory.¹⁰ It is well known that both physiological and physical factors significantly influence the accuracy and reproducibility of SUVs.¹¹ Variations in PET camera calibration, PET protocols (eg, scanning time point and image reconstruction algorithm), data analysis (eg, ROI position and size and background activity on contralateral hemisphere or cerebellum), and data settings (maximum and mean) can have more than a 50% effect on the measured SUV.¹² The comparison of SUV measurements, therefore, would require an inter-institutional calibration procedure to facilitate the exchangeability of SUVs between institutions. Although we agree with Drs. Langen and Galldiks that a quantitative PET parameter for clinical routine analysis would be useful, such a broadly validated procedure or LBR cutoff value, unfortunately, does not exist for [¹⁸F]-FET PET at present. Finally, we would like to indicate that a brain lesion with no or reduced [¹⁸F]-FET tracer uptake must be interpreted with caution, because they can also harbor low- or high-grade glioma tissue.¹,⁵

The second point discussed by Drs. Langen and Galldiks addresses the issue of the influence of a disrupted blood-brain barrier (BBB) on the specificity of [¹⁸F]-FET PET. In our study, we describe a correlation of [¹⁸F]-FET uptake to contrast enhancement (CE) on MRI, independent of WHO grading and brain lesion subtype (Fig. 1E).¹ Our observation should not lead to the conclusion that a high BBB permeability per se results in an [¹⁸F]-FET PET-positive brain lesion. We indicate that a positive [¹⁸F]-FET uptake might be the result of both a specific uptake into tumor cells and vascular cells¹³,¹⁴ and, at the same time, an additional unspecific uptake by [¹⁸F]-FET tracer retention because of various pharmacokinetic processes, including increased BBB permeability (eg, VEGF-mediated, inflammation, and necrosis), variable tumor blood volume, and perfusion effects. We agree with Drs. Langen and Galldiks that a BBB disruption in human gliomas per se only results in a slightly elevated [¹⁸F]-FET tracer uptake, which can be distinguished from high-grade tumor both visually and by LBR comparison. In the case of low-grade gliomas and the peripheral glioma-infiltrating zone of malignant gliomas, however, the LBR of the specific [¹⁸F]-FET tracer uptake may range in LBR levels of unspecific [¹⁸F]-FET uptake and may be not as sensitive as the visual approach. Therefore, corresponding MRI data sets should guide PET image analysis. Similar results were recently presented for [¹⁸F]-FLT.¹⁵ Additional kinetic analysis of dynamic [¹⁸F]-FET PET might potentially enhance the specificity of [¹⁸F]-FET PET imaging, because it was shown to provide valuable information for the differentiation of low- and high-grade gliomas even in lesions with low or diffuse tracer uptake; however, this method has to be validated for nonglial brain lesions.⁵


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We agree with the final supplementary comment by Drs Langen and Galldiks that $^{18}$F-FET uptake caused by reactive astrocytosis may be a relevant mechanism in $^{18}$F-FET PET–positive benign brain lesions. Such an $^{18}$F-FET uptake caused by reactive astrocytosis, however, is certainly not specific for and restricted to inflammatory or ischemic lesions, because reactive astrocytosis can also be a prominent feature in the tumor-infiltrating zone of gliomas.\(^{16}\)

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References


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