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LETTER TO THE EDITOR

Reply to "[^{18}F]-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 read with great interest the article entitled "[^{18}F]-fluoro-ethyl-L-tyrosine PET: a valuable diagnostic tool in neuro-oncology, but not all that glitters is glioma"[1] in *Neuro-Oncology* 2013;15(3):341–51. The experiences of the authors with ^{18}F-FET PET in a large unselected patient population with brain lesions are highly valuable for the readers and confirm present knowledge in many parts.

However, we need to express our concerns about the way in which a brain lesion was judged to be ^{18}F-FET positive or negative. As described by the authors, this was based on the visual analysis of a single nuclear medicine physician, and each tracer uptake above background was considered to be positive. This approach is different from that recommended by the guidelines of the European Association of Nuclear Medicine and German Society of Nuclear Medicine for brain tumor imaging using labeled amino acid analogues.[2,3] Both guidelines recommend the use of a threshold value of the lesion-to-brain ratio (L/B) to distinguish a positive result from nonspecific amino acid uptake. A biopsy-controlled study showed that the mean L/B of ^{18}F-FET uptake for the samples taken from peritumoral tissue was 1.2 ± 0.4, and a threshold of 1.6 separated best tumor from unspecific uptake.[4] The various thresholds that are recommended depending on the clinical problem are listed in the guidelines of the German Society of Nuclear Medicine.[2] Therefore, a considerable number of benign lesions in the article published by Hutterer et al. may be rated as ^{18}F-FET positive, although they would have to be classified as nonspecific according to the recommendation of the guidelines mentioned above. There is no doubt that benign lesions may exhibit increased ^{18}F-FET uptake, but it occurs presumably in a much smaller proportion than is claimed by the authors. In a recent study, we observed a mean L/B for nonneoplastic lesions of 1.4 ± 0.4 ($n = 25$),[5] which is similar to that observed by Hutterer et al.

Another objection concerns the authors' statement that the specificity of ^{18}F-FET uptake is limited by passive tracer influx though a disrupted blood-brain barrier (BBB), as indicated by contrast enhancement (CE) on MRI. An experimental study by Spaeth et al. showed that cryolesions as a model of pure BBB disruption without an inflammatory component leads to a L/B ratio of ^{18}F-FET uptake of 1.47 ± 0.09.[6] This slightly elevated uptake is below the threshold of 1.6 and can be separated from tumor tissue in the majority of cases. In agreement with this finding, ^{18}F-FET uptake in posttherapeutic changes with CE (eg, radiation-induced changes) is relatively low and can be separated from tracer uptake in recurrent tumors with high accuracy.[7] Furthermore, low ^{18}F-FET uptake has been reported in most contrast-enhancing abscesses and in ring-enhancing lesions after cerebral hemorrhage.[8] Thus, BBB disruption per se does not lead to significant ^{18}F-FET uptake. One reason for slightly increased ^{18}F-FET uptake in areas with BBB disruption may be the radioactivity in the blood pool resulting from the relatively slow urinary excretion of the tracer.[9] The strong correlation between CE on MRI and ^{18}F-FET accumulation is most likely to be caused by the fact that the degree of CE and specific ^{18}F-FET uptake is more pronounced in malignant tumors than in low-grade tumors and benign lesions and leads to the potentially misleading assumption of a causal relationship between both parameters.

Finally, we would like to comment on the authors' statement that the mechanism of ^{18}F-FET uptake in inflammatory brain lesions is currently unknown. Several experimental studies consistently reported that ^{18}F-FET shows no uptake in macrophages and in peripheral abscesses in contrast to L-[methyl-^{11}C]methionine and ^{18}F-2-Fluoro-2-deoxy-D-glucose.[9] In experimental studies of benign brain lesions, increased ^{18}F-FET uptake was observed in the vicinity of cerebral infarctions, abscesses, and hematomas in congruence with a reactive astrocytosis.[10–12] In humans, the histological finding of pronounced reactive astrocytosis was confirmed by biopsies of brain abscesses and demyelinating lesions that exhibited increased ^{18}F-FET uptake.[8] Therefore, high uptake of ^{18}F-FET in benign brain lesions is most likely attributable to reactive astrocytosis.

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